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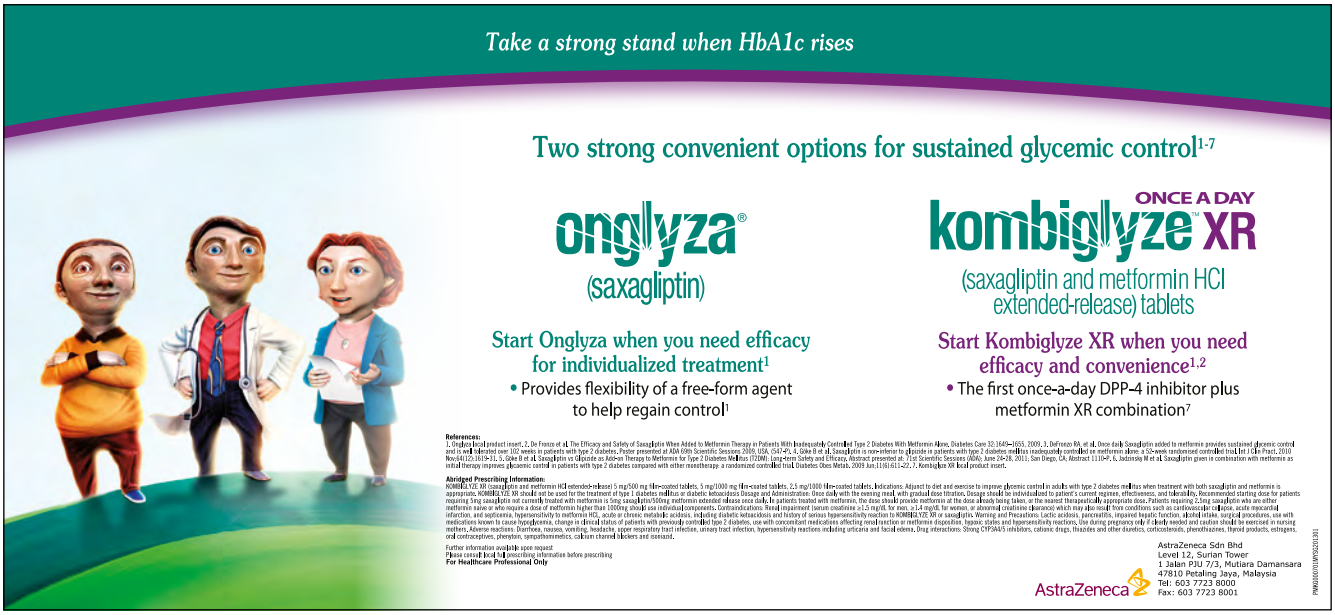
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BP lowering protects heart in early-stage kidney disease

Lianne Cowie

Lowering blood pressure is effective in preventing cardiovascular events in patients with mild or moderate kidney disease, according to a large meta-analysis.

"Specifically, blood pressure lowering per se, not the effects of a particular drug class... seems to be significantly associated with lower cardiovascular risk in early-stage chronic kidney disease, possibly suggesting the importance of blood pressure lowering as a driver of cardiovascular risk reduction," said the authors of the report.

The Blood Pressure Lowering Treatment Trialists' Collaboration, a project funded by the National Health and Medical Research Council of Australia, undertook a prospective meta-analysis of 26 randomized trials evaluating the efficacy of blood pressure lowering drugs against placebo, each other, or specific blood pressure thresholds. All were required to have a minimum of 1,000 patient-years of planned follow-up in each randomized arm. The trials included 152,290 individuals in total, 30,295 of whom had a reduced estimated glomerular filtration rate (eGFR) <60 mL/min/1.73m^2 at baseline. Pooled hazard ratios (HRs) for every 5 mmHg lower blood pressure were determined using a random effects model. [*BMJ* 2013;347:f5680 doi: 10.1136/bmj.f5680]

Every 5 mmHg reduction in systolic blood pressure among individuals assigned to an angiotensin converting enzyme (ACE) inhibitor or calcium channel blocker (CCB) reduced the risk of major cardiovascular events compared with placebo in individuals with (HR 0.83, 95% CI 0.76–0.90) and without (HR 0.83, 95% CI 0.79–0.88) a reduced eGFR. Moreover, the blood pressure lowering effects of the ACE inhibitors and CCBs were not significantly superior to those exhibited by diuretics/β-blockers when these were directly compared, and this was true for individuals with and without a reduced eGFR.

A meta-analysis has suggested that the broader use of BP lowering agents can play an important role in alleviating CV risk in patients with chronic kidney disease.

The authors remarked that their analysis provides clear evidence that a broad range of different blood pressure lowering regimens protect against adverse cardiovascular events in patients with and without chronic kidney disease.

"As people with chronic kidney disease are at greatly increased cardiovascular risk, the benefits of blood pressure lowering in this population are large," they concluded. "The broader use of blood pressure lowering drugs, along with other proved treatments such as lipid lowering, will both improve outcomes for affected individuals and help to reduce the escalating global burden of cardiovascular disease." MT

Over-regulation of e-cigarettes a potential threat to public health?

There has been much debate about the place of electronic nicotine delivery devices (e-cigarettes) in recent years, coincident with their ever increasing availability and popularity across the world. Medicines agencies in the West have become increasingly concerned with how to regulate these devices, which have the potential to act, and have been studied for their effectiveness, as nicotine replacement therapies. Interestingly, while e-cigarettes have their supporters, not all are in favor of their regulation as medicines. Associate Professor Jean-François Etter from the Faculty of Medicine, University of Geneva, Switzerland, provided the following perspective, based on excerpts of his presentation at the recent E-Cigarette Summit held in London, England.

Currently around the world, e-cigarettes are mainly regulated as consumer products or tobacco products, rather than medicines. However, impending regulation amendments in Europe and the US are set to play a very important part in the future of these controversial products. Having said this, there is no reason to expect that e-cigarette regulation will be the same in each country. On the contrary, I think regulations will differ between countries which take into local variations in factors such as stage of tobacco epidemic, history of tobacco regulation, political processes, weight of lobbies, and the state of development of the e-cigarette market.

I believe that future e-cigarette regulations in US and Europe will likely favor those who are best at lobbying governments. And this will be detrimental to the smaller and most innovative players in this market – the Chinese inventors and manufacturers. Big tobacco companies and big pharma will have advantages – they have so much expertise working within regulated environments. They also have a lot of money, large and established customer bases, and existing shelf space in shops. So they will be well placed to grab a large market share.

Currently in Europe, nicotine is regulated in a way that I think is a disaster for public health. Throughout most of the con-

tinent, the cheapest and most deadly form of nicotine – in smoked tobacco – is cheap and available everywhere, while smokeless nicotine is either banned or only available in medications (in patches or gums).

While nicotine replacement therapy (NRT) works, we know that differences in long-term quit rates between smokers given nicotine patches or gums are only marginally better (a few percentage points) compared with those given placebo versions.

The success of e-cigarettes is beginning to challenge this approach and I think the regulation of nicotine needs to be changed. The question is how? Is it a good idea to regulate the e-cigarette as a tobacco product and typically ban its use in public places, restrict advertisements, sales, and use by minors, etc? E-cigarettes are regulated as tobacco products in some countries, even though they do not contain tobacco. Nicotine is extracted from tobacco but does not contain tobacco. So it's not very logical.

There are several issues with placing stricter controls on e-cigarette use. I think the banning of e-cigarette 'vaping' in public places, for example, should require much stronger evidence that passive vaping is toxic or that it encourages non-smokers to become 'vapers' or smokers. Banning advertising, which helps to inform consumers, is also a problematic issue.

One thing most people agree on however is that there should be restrictions for minors. However, even this is not straightforward because minors who currently use nicotine or plan to use nicotine have no other choice but to smoke in many countries. So providing them an alternative way of getting nicotine is perhaps a controversial idea, but one that should not be rejected outright without further consideration.

I foresee several problems in regulating e-cigarettes as medicines. Importantly, I think it will kill innovation. Take nicotine gum and patches. They were invented in the 1970s and 1980s and have almost not evolved since then. It's not just the fault of the pharmaceutical industry but also the regulation framework which makes it so costly to improve a product. If such things as flavors are banned for example, then e-cigarettes will become less attractive. The other issue is what will happen with all the unlicensed products? They will not miraculously disappear. Enforcement may be very difficult, costly and ineffective. Unlicensed products may end up on a black market. Internet sales of unlicensed products will continue for which there will be no mandatory quality control.

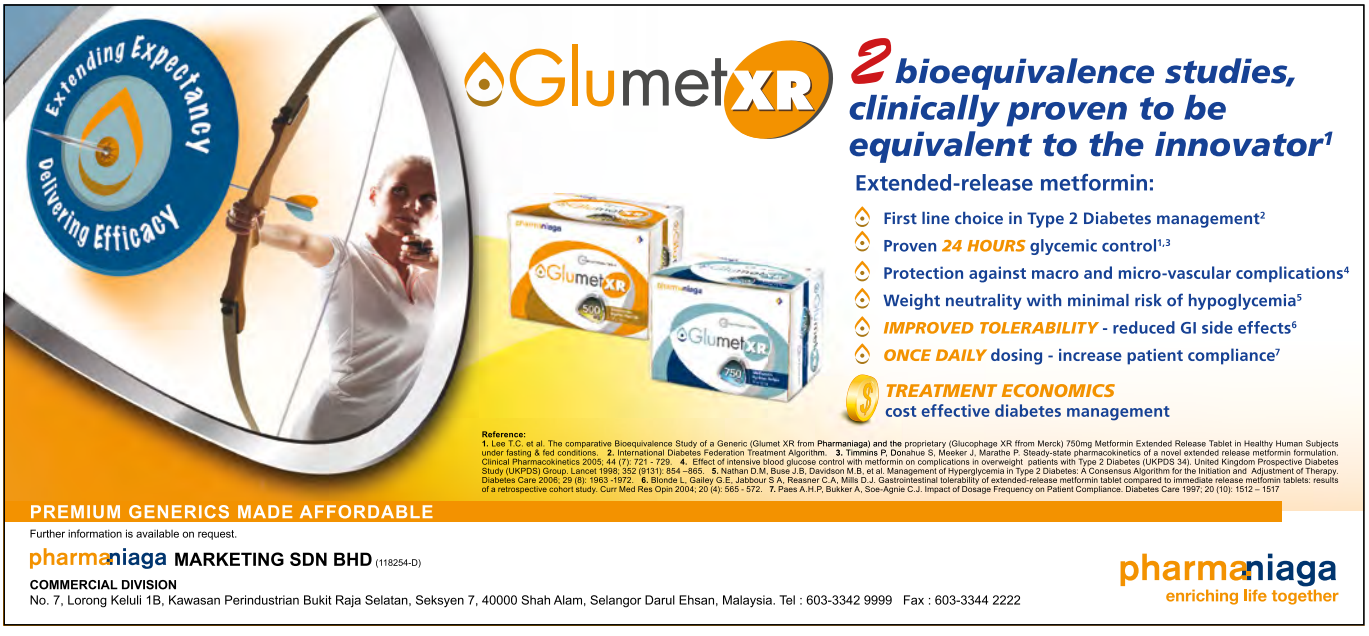
Other consequences of over-regulation will be a trend towards fewer e-cigarette users, because of higher costs. Fewer smokers will therefore quit and more will die. The entire e-cigarette market will become the domain of the tobacco industry because they are the only ones with e-cigarette products almost ready to be approved. I don't think this is a desirable outcome.

To conclude, I think e-cigarettes are a major innovation, a revolution in our field, that have the potential to save many lives. For regulators, I think we should always keep in perspective the huge number of deaths and disease and misery caused by smoking tobacco.

The relative risk is relevant compared with cigarettes because these products are used by smokers. They don't need to be 100 percent safe, only much safer than cigarettes. Their regulation as medicines or tobacco will be disproportionate, and the prohibition of unlicensed products will not be feasible or desirable.

The main danger for public health is the excessive regulation of e-cigarettes, not

e-cigarettes themselves. Laws need to be changed to make room for safe recreational nicotine products, even if they are used compulsively, and this is one of the most important things we have debated in public health in recent decades. MT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Ultrasound can improve patient outcomes in RA

Singapore researchers Drs. Peter Cheung and Manjari Lahiri from the division of rheumatology at the National University Hospital (NUH) say they have incorporated ultrasonography (uS) in their recently launched multi-disciplinary clinic that includes specialists, nurse educators, physiotherapists, occupational therapists and podiatrists.

In the Rheumatoid Arthritis through Education and Ultrasonography Study (RAEUS), researchers randomized 101 RA patients with stable disease and average disease duration of 6 years to either self-assessment through education and uS (n=51) or standard care (n=50). More than half the patients had joint damage and only 24 per cent had managed to achieve clinical remission, a treatment target.

After 6 months, clinical remission improved in the intervention arm from 24 percent to 46 percent compared with only a 4 percent improvement in the standard care group. Furthermore, 72 percent of the patients said looking at the sonograms helped them become more aware of their disease activity. MT

A*STAR, AstraZeneca tie-up to develop new antimicrobials

Gram-negative bacterial infections are responsible for about two-thirds of all deaths caused by hospital acquired infections and clinicians are fast running out of drugs to treat them, thanks to increasing drug resistance.

A joint research collaboration agreement between A*STAR's Experimental Therapeutics Centre (ETC), Exploit Technologies Pte Ltd (ETPL) and drug company AstraZeneca aims to address this growing public health problem by pooling resources and expertise to develop new antimicrobials.

ETC will contribute expertise in the discovery and optimization of lead compounds, while AstraZeneca will provide expertise in antimicrobial drug discovery. The three-and-a-half-year collaboration will focus on generating high quality preclinical drug candidates that can progress to clinical studies. The agreement also covers commercialization and licensing of any arising intellectual property.

"The synergy between our novel approaches in lead generation and optimization and AstraZeneca's established track record in anti-infectives would give us both a fighting chance in tackling the challenge of penetrating the Gram-negative bacterial armor," said ETC chief executive Professor Alex Matter. MT

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Aripiprazole may improve methamphetamine-induced psychosis

Seah Yee Mey

A randomized controlled trial has found aripiprazole to be generally well tolerated and a safe alternative for treatment of psychotic symptoms arising from methamphetamine use, says a speaker at the recent annual meeting of the International Society of Addiction Medicine.

Symptoms of methamphetamine-induced psychosis include delusions, thought disorders, hallucinations, psychomotor agitation, hyperawareness, physical aggression and irritability, said Dr. Ahmad Hatim Sulaiman, of the Faculty of Medicine, Universiti Malaya.

Methamphetamine-dependent patients with a history of psychosis were enrolled in the double-blind study. They were randomly assigned to receive 5-10 mg of aripiprazole daily (n = 19) or placebo (n = 18) for 8 weeks, said Ahmad Hatim, who is also the lead author of the paper. Participants were then evaluated on a weekly basis. [*Int J Psychiatry Clin Pract* 2013;17(2):131-8]

Aripiprazole reduced the severity of psychotic symptoms, based on a decrease in Positive and Negative Syndrome Scale (PANSS) scores from the baseline 44.9 (±10.6) to 38.0 (±10.0) at the end of 8 weeks ($P < 0.05$); however, it was no more effective than placebo in reducing methamphetamine use. Ahmad Hatim said aripiprazole was generally safe and well tolerated.

This study follows on the heels of an earlier open-label study of aripiprazole in 49 patients with methamphetamine dependence and psychotic co-morbidities. [Bull Clin Psychopharm 2012;22(2):121-9] The 2-week prospective study also saw a mean reduction in PANSS scores of 27.6±21.4 ($p<0.05$), with generally few adverse reactions to aripiprazole.

Heavy methamphetamine use as well as comorbid major depressive, bipolar and antisocial personality disorders are risk factors for lifetime methamphetamine-induced psychosis in Malaysian users, said Ahmad Hatim, citing another study he led which recruited patients from University Malaya Medical Centre and a drug rehabilitation centre in Papar, Sabah. [Compr Psychiatry 2013. doi: 10.1016/j.comppsych.2013.01.003] Certain genetic polymorphisms in a brain-derived neurotrophic factor and an enzyme involved in lipid degradation also appear to be correlated with methamphetamine dependence. [*Pharmacogenomics* 2013;14(5):505-14; Brain Res 2010;1357:91-6]

Methamphetamine, also known as 'ice,' 'crystal,' 'glass' or 'syabu,' triggers the release of the neurotransmitter dopamine, Ahmad Hatim said. This affects the cerebral cortex, causing heightened energy and a sense of euphoria, and also affects the limbic regions, or pleasure centers, of the brain. Once its effects wear off, the withdrawal symptoms include depression, paranoia and aggression.

Methamphetamine addicts will eventually need to administer higher doses to achieve the same pleasurable effects as they develop tolerance to the drug, leading to strong dependence when used long term.

Chronic use of methamphetamine can cause dopamine depletion. Irreversible neu-

ronal changes can also occur, manifesting as psychiatric symptoms, cognitive impairment, memory loss and behavioral deficits, he said.

Besides psychotic and neurological symptoms, long-term methamphetamine abuse also negatively affects cardiovascular and respiratory health. Dermatological manifestations include self-induced skin picking, abscesses and skin ulcers. Both acute and chronic methamphetamine abuse have also been associated with hepatocellular, gastrointestinal and dental damage. MT

Integrating HIV therapy with addiction treatment: Progress and barriers

Seah Yee Mey

Combining opioid substitution therapy with efforts to reduce harm amongst HIV-positive individuals shows promising outcomes, but many obstacles still exist in implementing integrated treatment, says an infectious disease specialist.

Speaking at the annual meeting of the International Society of Addiction Medicine, Professor Adeeba Kamarulzaman, of the department of medicine, Faculty of Medicine, Universiti Malaya, reported on the outcomes of pilot methadone maintenance treatment (MMT) programs that were established in Kajang, Selangor, and Pengkalan Chepa, Kelantan, prisons. HIV-infected prisoners who participated in the MMT program were more likely to be retained in the program if they were being administered methadone (>80 mg) daily upon release from incarceration. [*Bull World Health Organ* 2013;91(2):124-9] After release, participants had problems accessing treatment, either because they were harassed by police officers at MMT sites or were forced to relocate due to corrective police orders.

There were also patient-, staff- and institutional-level factors affecting successful implementation of the MMT program, said Adeeba. Most patients were self-stigmatized and unwilling to disclose their HIV status to their families. Tuberculosis (TB) incidence was also high in MMT participants; anti-TB agents or antiretroviral (ARV) therapy can both reduce methadone levels.

At the staff level, prison clinicians were initially uncomfortable treating addiction; however, this was resolved through supervision and training that emphasized the rationale of the MMT program, as well as dosage, pharmacokinetic interactions and adverse side effects of methadone. Logistical issues pertaining to patients' transitional care were also addressed. Repeated educational sessions for prison inmates and staff were needed due to high turnover rates.

The success of the MMT program was also largely due to support from the Director-General of the Prisons Department. Institutional-level hindrances included uncertain prisoner release dates, community-based MMT dose reductions and depleted stocks of ARV.

Nevertheless, there is always hope. Adee-

ba shared promising preliminary outcomes from Project HARAPAN, a randomized controlled trial to look at outcomes in HIV-positive opioid-dependent prisoners who receive methadone alone or in combination with behavioral intervention strategies. Project HARAPAN has currently enrolled about 300 participants, and thus far the 6-month retention rate of participants is highest for those receiving either MMT only or both MMT and behavioral intervention, compared to participants in either the control group or those who only had behavioral intervention.

Adeeba also referred to the work done by Dr. Norsiah Ali and her team at the Ministry of Health Tampin Health Clinic in Negeri Sembilan, where MMT is available, as well as other forms of comprehensive care such as needle and syringe exchange programs, ARV therapy, and mental health screenings and treatment. Psychosocial support in the form of welfare assistance is also provided, in addition to opportunities for employment and community engagement.

The outcomes from the comprehensive care provided to injecting drug users in that region is very positive, Adeeba said, with MMT retention rates of up to 84 percent at 6 years of follow-up. All patients eligible for ARV therapy are also receiving treatment, and no HIV seroconversion has been observed amongst uninfected patients who first attended the MMT program.

Injecting drug users have greater morbidity and mortality rates than other populations at risk for HIV. [Lancet 2010;376:367-87] Amongst injecting drug users, ARV therapy has been associated with significant reductions in HIV-related mortality, said Adeeba, citing the longitudinal HIV Epidemiologic Research on Outcomes (HERO) study. [*Clin Infect Dis* 2005;41(6):864-72] Opioid substitution therapy is also strongly associated with improved adherence to ARV therapy and better health outcomes among HIV-positive injecting drug users, she said.

Unfortunately, injecting drug users disproportionately under-utilize voluntary counseling and therapy, primary care and ARV therapy, especially in countries that have the largest burden of HIV amongst this population. Seeking out and testing high-risk people requires active outreach and overcoming the stigma surrounding substance abuse and HIV, Adeeba said, agreeing with a recent review by Strathdee et al on the obstacles in reaching out to injecting drug users. [*Curr Opin HIV AIDS* 2012;7(4):320-5]. MT

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ASEAN cardiology meeting here in June

Saras Ramiya

An important regional conference on cardiology covering a wide range of topics will be held in Malaysia next year.

The 20th ASEAN Federation of Cardiology Congress (AFCC) 2014 will meet at the Kuala Lumpur Convention Centre from 12 to 15 June.

According to organizing chairman Dato' Dr. Rosli Mohd Ali, "The main feature of this conference is the Cardiovascular Interventions Symposium with Live Transmission from the National Heart Institute (IJN) and overseas centers."

Several joint symposia that will be held include those in collaboration with the American College of Cardiology (ACC), Asian Pacific Society of Interventional Cardiology (APSIC), European Society of Cardiology (ESC), EuroPCR (the official congress of the European Association of Percutaneous Cardiovascular Interventions) and Society for Cardiac Angiography and Interventions (SCAI).

Key opinion leaders (KoLs) from the US and Europe, including the presidents of ESC and ACC, will be here to share their knowledge. The AFCC-ESC Symposium will involve a large faculty of top KoLs from Europe, Rosli said.

A panel discussion with local KoLs will be held to discuss the guidelines and best practices in Europe, which may be adapted for local practice. This interactive session is part of the AFCC-ESC Symposium.

In addition, continuing medical education (CME) sessions will be held. They will include the SCAI Fellows Course, Echocardiography Course and Hands-on Pediatric Interventional Workshop. The SCAI Fellows Course is jointly organized by SCAI and the National Heart Association Malaysia (NHAM).

Following the tradition of AFCC, the Fellows Convocation of the ASEAN College of Cardiology (FAsCC) will be held with full ceremony. Delegates from various member countries are expected to participate, Rosli said.

He said the scientific content will cover all the disciplines in cardiology, with a good blend of international and ASEAN perspectives delivered by prominent speakers. There will be state-of-the-art updates on cardiac arrhythmias, cardiac imaging, cardiac rehabilitation, coronary heart disease, general cardiology, hypertension, interventional cardiology, lipid, pediatric cardiology, preventive cardiology, valvular heart disease and women's health.

There will also be a good mix of plenary sessions, symposia, interactive sessions, pre-congress workshops and joint symposia. There will also be simultaneous international and local live transmissions of coronary, valvular and vascular interventions for adult and pediatric patients, Rosli said.

A new feature of the AFCC 2014 is the mobile app, which will help delegates plan their attendance of the sessions. The app will pro-

vide latest updates of AFCC proceedings. Apart from conference proceedings, the app will provide news, city guide and other tourist information with assistance from Tourism Malaysia. This information will be made available to delegates prior to their arrival in Kuala Lumpur.

The social program includes a gala dinner where, in line with AFCC tradition, delegates from each country will entertain the participants with performances. There will also be a fun run to make AFCC a healthy event.

For further information on AFCC 2014, please go to: ***www.afcc2014.org.*** MT

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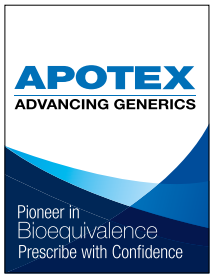
Patients can play a big role in improving healthcare safety



Seah Yee Mey

Discussions and decision-making on healthcare safety issues can and should include patients' voices in various capacities, a WHO officer says.

Speaking at a patient safety conference jointly organized by the Malaysian Society for Quality in Health (MSQH) and the Malaysian Ministry of Health, in collaboration with the US ECRI Institute, Nittita Prasopa-Plaizier, WHO's technical officer and lead for WHO's Patients for Patient Safety (PFPS) program, said it is not a question of whether patients should be engaged in discussions of their own safety, but how they can contribute.

In 2005, WHO issued a challenge to put patient safety on the healthcare agenda of the world's governments. Professor Chris Baggoley, chief medical officer for the Australian government, has shown that patient engagement can be embedded into national policy. In Australia, patient and consumer engagement is one of 10 national quality standards.

Patient engagement in safety issues means treating patients as partners and sharing leadership roles with them, said Prasopa-Plaizier. The PFPS program believes that by sharing patient experiences and expertise, individuals and organizations can learn from each other and improve. As such, patients can be engaged as advocates and catalysts for change simply by telling their stories and putting a human face to safety statistics, she said. Patients can also act as advisors on professional, accreditation and regulatory committees, thereby contributing to policy development, or as educators of students and health professionals, or as research collaborators and co-authors.

Some patients have founded organizations to support, educate and empower other patients. For instance, Dr. Purnamawati Pujiarto from Indonesia, leads an NGO that runs a health education program for parents to educate them on child health, and rational prescription and use of medication. Hussain Jafri founded Alzheimer's Pakistan, a national organization for patients and caregivers as a result of his experience taking care of his afflicted grandfather.

Patients can also actively champion to support WHO programs and policies, said Prasopa-Plaizier. Some patients are international reviewers of the WHO Patient Safety Research Small Grants program, which supports 24 projects in 22 countries. Robinah Kaitiritimba

from Uganda is an example of a PFPS champion who works with national and international policymakers to include patients' voices and civil society in strengthening health systems.

PFPS worked to introduce patient participation in WHO's First Global Patient Safety Challenge aimed at reducing healthcare-associated infections worldwide through the promotion of best practices in hand hygiene and infection control. According to a recent WHO survey, in 260 facilities across 41 countries, patient participation was perceived as useful in contributing to hand hygiene improvement.

PFPS also brought the patient's voice to the International Conference on Radiation Protection in Medicine meeting in 2012. The patients were invited to present to the Radiation Safety Standards Committee of the International Atomic Energy Agency (IAEA) the following year – the first time patients have ever presented to IAEA high-level regulators.

Engaging patients in healthcare issues is not without its challenges, Prasopa-Plaizier cautioned. Patient engagement can refresh the trauma experienced by those involved, and increase emotional turmoil for patients, caregivers and providers. It may also increase fear and distrust by patients or their families towards accessing healthcare providers, staff or services, and may be damaging to individual or organizational reputations.

However, the benefits are well worth the effort, to be able to hear directly from those involved in the healthcare system and understand the perspective of patients and their families. This promotes communication and teamwork between healthcare providers and patients, resulting in a more positive patient safety culture. Safety or quality improvements can also be identified directly by those who have had firsthand experience, and patient- or family-centered solutions can be developed, she concluded. MT

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MTMAY15-31-13/001

Diabetes treatment needs to be individualized

Seah Yee Mey

Treatment approaches for diabetes, which has complex pathophysiology, should be tailored to each patient, says a consultant endocrinologist.

Based on the outcomes of several large long-term trials, namely Action to Control Cardiovascular Risk in Diabetes (ACCORD), Action in Diabetes and Vascular Disease – Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE), and the Veterans Affairs Diabetes Trial (VADT), the American Diabetes Association (ADA), the American College of Cardiology Foundation and the American Heart Association issued a position statement suggesting that individualized glycemic targets may be appropriate for some patients. [*J Am Coll Cardiol* 2009;53(3):298-304] This concept is still poorly applied in clinical practice, said Dr. Zanariah Hussein, perhaps due to uncertainty on how to integrate personalized treatments with accepted standards of care as laid out in clinical practice guidelines (CPG).

Current treatment goals for glycemic control in Malaysians include HbA_{1c} levels <6.5 percent, preprandial capillary plasma glucose of 4.4-6.1 mmol/L and peak postprandial capillary plasma glucose of 4.4-8.0 mmol/L. However, these targets are difficult to achieve in some patients, and approximately three quarters of Malaysian diabetics are not within the recommended limits, she said. She noted that the 2009 Malaysian CPG for management of type 2 diabetes mellitus also advised individualization of glycemic targets to minimize risk of hypoglycemia. This is in step with the recommendation by the ADA and European Association for the Study of Diabetes (EASD) that a less stringent approach to managing hyperglycemia is appropriate for certain patient populations. [*Diabetes Care* 2012;35(6):1364-79]

Patients of advanced age or have long-standing diabetes, history of severe hypoglycemia, or micro- or macrovascular complications may benefit from HbA_{1c} goals that are less stringent than the recommended target, while normal glucose levels can be aimed for in newly diagnosed patients, Zanariah said. Other factors to consider when individualizing HbA_{1c} targets include diabetes type, pregnancy status, diabetes medications, presence of cardiovascular risk factors and other comorbidities.

One of the lessons to be learned from trials such as ACCORD, ADVANCE and VADT is that it is difficult to get significant gains in patients with complication, or who have had diabetes for a long duration if the intervention is too late. Therefore, patients need to be treated more appropriately at an early stage

of the disease, as suggested by the UK Prospective Diabetes Study, said Zanariah. Since type 2 diabetes affects people of all ages, one of the approaches physicians can take is to personalize HbA_{1c} targets based on age, with a stricter goal for younger patients. [*Diabetes Metab Res Rev* 2010;26(4):239-44]

As with the ADA, EASD and the UK National Institute for Health and Care Excellence treatment algorithms, the Malaysian CPG also call for lifestyle modifications as the first step in managing type 2 diabetes. [Type 2 Diabetes – newer agents. NICE clinical guidelines 2009. ***http://guidance.nice.org.uk/cg87*** Accessed on 28 November] Subsequent steps involve choosing the appropriate antidiabetic medication.

Zanariah acknowledged that with the multitude of oral and injectable antidiabetic agents available, and multiple combinations of therapies, it is difficult to select the right individualized treatment. The different types of antidiabetic agents attempt to address the different pathophysiological defects that lead to hyperglycemia, she said. A patient-centered approach to selecting the appropriate medication should consider several factors including patient's hypoglycemic risk and weight, as well as the glycemic efficacy, major side effects and cost of selected agents, she said.

While clinical data supporting individualization of treatment is not yet available, the multicenter Glycemia Reduction Approaches in Diabetes (GRADE) study that aims to compare glycemia-lowering effectiveness and patient-centered outcomes of commonly used diabetes medications in combination with metformin is currently underway. [D*iabetes Care* 2013;36(8):2254-61]

Although management of type 2 diabetes can be complicated with multiple evidence-based treatment guidelines and medications, Zanariah reminded physicians that modern diabetes care should focus on partnerships between patients and healthcare providers to create personalized care with the aim of improving patients' long-term wellbeing and psychological health.

Zanariah was speaking at the recent Diabetes Asia conference organized by the National Diabetes Institute. MT

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The benefits and superiority of breastfeeding

Breast milk is the best food for infants as it provides the best nutrition, immune defence and protection from diarrhea, colic, regurgitation and constipation for infants. Breastfeeding should be initiated at once after or within one hour of delivery. Good maternal nutrition is essential to prepare and maintain breast-feeding. Mothers should be reminded the benefits of breast milk, and also it is the most economical food for infants. Working mothers should also be encouraged to continue breastfeeding even after they resume their full time jobs. The introduction of partial bottle feeding will have a negative effect on breastfeeding. Before using infant formula, a mother should be aware of the financial and social implications and the possible health hazards of formula feeding. Inappropriate food or feeding method may lead to health hazards. However, if mothers decide to supplement with an infant formula or not to breastfeed at all, they should seek advice from their health professionals before starting the use of infant formula. Mothers should be professionally instructed on the importance of infant feeding methods, including the cost of infant formula and the health hazards of inappropriate foods or feeding methods. Mothers who are unable to breastfeed should seek professional advice. It is important to warn mothers of the difficulty of reversing a decision not to breastfeed.

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Blood clotting not just a 'Western' disease

Angeline Woon

Asians need to be more aware of venous thromboembolism (VTE) in terms of diagnosis and prophylaxis use, says a local specialist.

Although worldwide incidences of thrombosis are largely similar, thromboprophylaxis rates in Asia are lower, probably because Asians view it as a disease affecting only people in the West, said Dr. Jameela Sathar, a senior consultant hematologist at Ampang Hospital, Kuala Lumpur.

VTE comprises deep vein thrombosis (DVT), when a blood clot forms in the deep veins, usually in the legs; and/or pulmonary embolism, when a blood clot is dislodged and causes a blockage in the lungs or pulmonary vessels.

"VTE is often clinically silent and, in many cases, the first sign of the disease is a sudden, fatal pulmonary embolism," Jameela said. VTE, she added, is a leading cause of death worldwide, and after ischemic heart disease and stroke, is the most common vascular disease.[*J Gen Intern Med* 2006;21:722-7] Pulmonary embolism causes about a third of VTE deaths and is the leading cause of hospital mortality. [*Thromb Haemost* 2007;98(4)756-64]

Part of the problem in diagnosis is the non-specific signs and symptoms of the disease. Patients with DVT typically present with painful and swollen legs, with an increase in warmth and tenderness along the deep vein when palpated, similar to other diseases like cellulitis. Patients with pulmonary embolism may present with acute shortness of breath, chest pain, tachychardia or may be coughing blood, which can also be symptoms for other diseases such as pneumonia.

The best way to diagnose VTE is by Doppler ultrasound for DVT and computer tomography pulmonary angiograms for pulmonary embolism.

Once a diagnosis has been made, traditional treatment options include a dual-drug combination of daily injections of low-molecular weight heparin and warfarin, an oral vitamin K antagonist.

"This standard treatment approach can be complex for physicians and burdensome for patients," said Jameela. Among the challenges are prolonged hospitalization, the need for injections and a difficult medication schedule. Warfarin works by inhibiting vitamin K-dependent clotting factors, so patients have to avoid certain common foods such as green, leafy vegetables. Many common medications are contraindicated as well.

In addition, patients need to undergo frequent blood monitoring due to warfarin's narrow therapeutic index. If patients receive too little of the drug, they may get another clot; too much and they may bleed excessively.

Warfarin therapy lasts for at least 3 months.

Other treatments include rivaroxaban, a novel oral factor Xa inhibitor that is more specific in action and, thus, has minimal food and drug interactions.

Jameela said patients would benefit from this drug as it does not involve injections or regular monitoring, and has been shown effective in the EINSTEIN-PE trial. [*N Engl J Med*. 2012;366(14):1287-97]

She was speaking at the announcement of a new indication for rivaroxaban in Malaysia for the treatment of pulmonary embolism and the prevention of recurrent DVT and pulmonary embolism in adults. Previous indications for rivaroxaban in Malaysia included stroke prevention in atrial fibrillation, treatment of DVT and the prevention of recurrent VTE, and the prevention of VTE following elective hip or knee replacement surgery. MT

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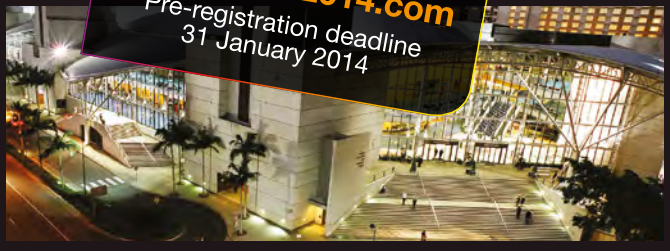

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Prostate Health Index improves prostate cancer detection in Chinese men

Jackey Suen

A recent study confirms that the Prostate Health Index (phi) offers more accurate detection of prostate cancer than serum levels of prostate-specific antigen (PSA) alone, helping to avoid more than 40 percent of unnecessary biopsies in Chinese men. [*Int Urol Nephrol* 2013; e-pub 18 Oct, doi: 10.1007/s11255-013-0582-0]

"In Hong Kong, prostate cancer is mostly diagnosed by case finding, as shown in our study of 120 patients," reported Professor Anthony Chi-Fai Ng of the Department of Surgery, Chinese University of Hong Kong, at a press conference. "Physician-initiated case finding is the main approach for early detection of prostate cancer."

"However, elevated serum PSA level is not specific for prostate cancer," he pointed out. "As a result, many patients have to undergo transrectal ultrasound-guided prostatic biopsy, which can lead to sepsis and other complications."

The phi, developed by US researchers, calculates the probability of prostate cancer based on levels of total serum PSA, free PSA and a prostate cancer-specific PSA precursor called [-2]proPSA. The US FDA approved its use in 2012 for the detection of prostate cancer in men >50 years of age with a serum PSA level of 2-10 ng/mL and negative digital rectal examination (DRE) findings.

"We recently evaluated the accuracy of the phi in the local population," said Ng. "Our retrospective study included 230 men older than 50 years with mildly elevated serum PSA level [4-10 ng/mL], who had a negative DRE and proceeded with prostate biopsy. Twenty one patients were confirmed to have prostate cancer."

Ng and colleagues analyzed the participants' serum samples collected before biopsy and compared the performance of the phi with other PSA parameters (total PSA, PSA density, free-to-total PSA ratio, [-2]proPSA, and [-2]proPSA-to-free PSA ratio) in detecting prostate cancer.

"The phi was the best predictor of the prostate biopsy results, with a specificity of 49.76 percent. If the phi was used for screening, we could have avoided unnecessary biopsies in 104 patients [45.2 percent] while maintaining a sensitivity of 90 percent. In contrast, using other parameters could have avoided unnecessary biopsies in only 36 to 88 patients," he said. "These results are comparable to US findings."

"Testing of the phi is currently available in the private sector only," noted Ng. "Ongoing prostate cancer research focuses on risk allele identification, and new methods of urine analysis and magnetic resonance imaging." MT

Education helps dialysis patients stay in employment

Christina Lau

Educating patients with chronic kidney disease (CKD) about the condition and its treatment helps them stay in employment after the commencement of dialysis, according to a study by the Chinese University of Hong Kong (CUHK).

The study showed that despite having the ability to work, 39.1 percent of CKD patients on peritoneal dialysis (PD) are unemployed. "This is much higher than the unemployment rate of the general population in Hong Kong, currently at 3.3 percent," pointed out Professor Philip Li of CUHK's Division of Nephrology.

Li and colleagues surveyed 383 CKD patients on PD at the Prince of Wales Hospital. The patients had been on PD for an average of 3.6 years, with 15.1 percent on machine-assisted home PD. Nearly half of the patients had diabetes.

"In patients aged 18 to 60 years who were not housewives, only 23.4 percent were engaged in full-time employment, and 9.4 percent were working part-time," Li reported.

"Participation in our Predialysis Education Program was conducive to their continued employment after the commencement of dialysis," he continued.

The program helps patients with mid- and late-stage CKD and their family members understand the disease, kidney failure and renal replacement therapy, as well as currently available nephrology services. Enlisting doctors, nurses, medical social workers, dietitians and members of patient self-help groups as educators, the program also aims to build trust between CKD patients and the nephrology team.

"Patients who took part in the program at least 6 months before the start of dialysis had an employment rate of 43.5 percent, compared with 16.7 percent of those who did not receive the education," said Li.

Given these results, the CUHK researchers encourage patients with mid- and late-stage CKD to participate in the education program, as it helps them achieve better rehabilitation and employment status.

"The use of machine-assisted home PD also contributed to a higher employment rate in CKD patients on PD," Li noted. "In our survey, almost 60 percent of these patients were employed."

"Employers are encouraged to provide better working environments and flexible schedules for dialysis patients," he added. MT

Number of daily smokers falls

Christina Lau

The number of daily smokers in Hong Kong has continued to fall, according to the latest survey by the Census & Statistics Department.

The percentage of daily cigarette smokers aged 15 years or above has decreased from 11.1 percent in 2010 to 10.7 in 2012. This represents a continued downward trend since 2002, when the corresponding rate was 14.4 percent.

"The survey results indicate the effectiveness of the comprehensive tobacco control measures adopted by the government," said Professor Sophia Chan, Under Secretary for Food & Health. "Although the prevalence of daily cigarette smoking in Hong Kong continues to be one of the lowest around the world, we cannot afford complacency."

An area of concern is the 64.5 percent of daily smokers who started smoking weekly at the age of 10-19. On average, daily smokers consumed 13 cigarettes per day.

Although 70.3 percent of all current smokers were aware of the smoking cessation services currently available in Hong Kong, only 39.1 percent of them had tried the services. The awareness and use of such services were lower among male smokers.

Despite the extension of statutory no-smoking areas to open-air public transport facilities in 2010, 88 percent of daily smokers reported no change in their quantity of smoking. MT

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Live poultry market closure halts H7N9 spread

Jenny Ng

Public health researchers have confirmed that the closure of live poultry markets (LPMs) in the urban areas of China can dramatically reduce the number of human infections of avian influenza A (H7N9).

The new study, a collaboration between the Chinese Center for Disease Control and Prevention and the University of Hong Kong, showed that closure of LPMs in four of the hardest hit outbreak areas in China (Shanghai, Hangzhou, Huzhou and Nanjing) reduced the incidence of poultry-to-human infections at a rate that could not be explained by seasonal factors. [*Lancet* 2013, e-pub 30 Oct, doi:10.1016/S0140-6736(13)61904-2]

The researchers used data from 60 laboratory-confirmed human cases of H7N9 to construct a statistical model that included constant pre- and post-closure rates of infection. The cases were identified from the four cities since the closure of 780 LPMs in April 2013 until 7 June 2013.

LPM closure was found to reduce the mean daily number of human infections by 99 percent in Shanghai and Hangzhou, and by 97 percent in Huzhou and Nanjing. The estimated incidence of infection was substantially reduced within 2 to 3 days after the closures. Furthermore, the researchers estimated the mean incubation period of human H7N9 infection to be 3.3 days, vs the 1 week as was previously suggested.

In a sensitivity analysis, absolute humidity, a common climatic factor strongly associated with influenza transmission, was found to have no effect on the estimated incidence of H7N9 infection after LPM closure.

"In the short term, LPM closure should be rapidly implemented in areas where the virus is identified in live poultry or people. In the long term, evidence-based discussions and deliberations about the role of market rest days and central slaughtering of all live poultry should be renewed," concluded the researchers.

Although previous analyses have supported the closure of LPMs, this is the first one to provide robust quantitative evidence against the millennia-old tradition of trading live birds. However, such a large-scale closure could result in serious economic losses.

As mentioned in an accompanying commentary, the underlying epidemiological and socioeconomic systems are complex, and LPM closure might not have been the most important cause of the reduction in H7N9 incidence. An appropriate solution should result in a sustainable reduction in disease spread while protecting livelihoods and food security. [*Lancet* 2013, e-pub 31 Oct, doi:10.1016/S0140-6736(13)62109-1]

From a public health standpoint, given the estimated 35 percent mortality among hospitalized cases, and up to 1 percent mortality among symptomatic cases in the recent H7N9 outbreak, LPM closure may be a potentially lifesaving intervention despite the adverse economic effect. MT

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NTU nanomedicine research institute first of its kind in the region

Rajesh Kumar

Southeast Asia's first nanomedicine research institute set up at the Nanyang Technological University (NTU) will work to find innovative nano solutions to diabetes, cardiovascular, ophthalmology and skin therapeutics.

The $60 million Nanotechnology Institute @ NTU is headed by Professor Subbu Venkatraman, chair of NTU's School of Materials Science and Engineering, with eminent Professor Chad Mirkin of the Northwestern University as the chairman of its advisory committee.

Mirkin's involvement in the institute represents a big coup for the NTU. In addition to being a scientific advisor to US President Barack Obama, Mirkin is a celebrated nanotechnology expert with more than 80 national and international awards and 930 patents to his credit.

NTU has already produced some 'first-in-the-world' solutions using nanomaterials for cardiovascular and ophthalmological diseases. However, the university's Provost Professor Freddy Boey said there were many more unmet medical needs that could be addressed.

"While there are current drugs to tackle the diseases of today, they may not be the most effective in their current form. For example, by changing the packaging and delivery of a drug into a nano-sized form, we can prolong the period of which the drug stays in a body, reducing both the frequency and amount of drugs needed to treat the affected body part," said Boey.

Such innovative solutions can only be found through a strong interdisciplinary approach in research, said Subbu, founding director of the institute.

(L-r) Prof. Subbu Venkatraman, Prof. Chad Mirkin, Prof. Freddy Boey.

"For example, the new glaucoma nanomedicine was only developed through joint collaboration between myself, Prof. Boey and a clinician-scientist, Associate Professor Tina Wong, from the Singapore Eye Research Institute."

The nanomedicine is made by encasing the usual anti-glaucoma drug in millions of nano-sized capsules, which then degrade over a few months to release the drug. These capsules are about 100,000 times smaller than a grain of rice.

"A prolonged timed-release drug delivery nanomedicine product did not exist until now, and it would not have been possible without inputs of medical doctors and strong materials science knowledge," said Subbu.

Similarly, balloon angioplasty and stenting can be further improved with a new gel developed at the NTU. The gel contains millions of timed-release nano-sized capsules which contain anti-restenotic agents.

The International Institute of Nanotechnology (IIN) at the Northwestern will be the

main collaborative partner of the new Nanotechnology Institute @NTU, while other notable collaborators include Professor Lenny Rome of the California Nanosystems Institute (CNSI) and Prof Shlomo Mogdassi of Hebrew University. MT

Medicolegal Tips

Writing reports following an adverse event

Dr. Janet Page
Medicolegal adviser at the Medical Protection Society
www.medicalprotection.org

A serious untoward incident may trigger any one of a number of investigations, including a Coroners Inquiry, complaint or clinical negligence claim, police investigation or Medical Council inquiry, to name but a few. The incident report may be the starting point for such investigations.

Reports relating to patients under your care should be a factual account of your personal involvement and would not normally include your opinion about the care provided. If you are asked to comment about such matters, you should do so in a separate document. Any opinion provided should be confined to matters within your area of expertise and supported by evidence.

Preparing the report

In preparing a report, you should ensure that you have access to all relevant documents so that your report is comprehensive, addresses all the issues raised and is consistent with the supporting documentation. You are entitled to rely on the medi-

cal records, your recollection of events and your usual practice in similar circumstances. The sooner after the event that the report is drafted the better and more reliable your recollection of events is likely to be.

Your involvement in the case

You have a professional obligation to ensure any reports you write are accurate and true to the best of your knowledge, and that they are not misleading or overtly critical of colleagues. [MCHK Code of Professional Conduct, paragraphs 19 and 26]

Your report should be a comprehensive account of your involvement in the patient's care. An introductory paragraph setting out the capacity and circumstances in which you attended the patient is helpful to put your report into context. This should be followed with a chronological, factual account of your personal involvement in the patient's care, with reference to dates and times of each contact and identifying, by name and role where possible, any other healthcare personnel involved. You should record the history taken, examination findings including results of investigations, working diagnosis and management plan for each contact, where appropriate.

Your report should be written using language and terminology appropriate for its purpose and the intended recipient, and specialized terminology should be clearly explained.

Gaining consent

Before writing a report, you should ensure you are clear as to the purpose of the report and the authority under which it is requested. Where appropriate, you should ensure you have the patient's consent (or in the case of deceased patients, the personal representative or next of kin) before disclosing the report. You should not disclose information to a patient's employer or an insurance provider without the patient's express consent.

Consent is not required in circumstances in which you have a statutory duty to provide the requested information, such as for the purposes of a Coroner's investigation or to comply with an Order of the Court. Exceptionally, you may be justified in disclosing information without consent if there is an overriding public interest in you so doing, for example where your failure to disclose would put others at risk of serious harm. If in doubt, you should seek advice before proceeding.

Seeking advice

Reports following serious untoward incidents can lead to a number of potential investigations in which your actions could come under scrutiny. To ensure that you are clear about your obligations or for guidance about a specific report, you should seek professional advice from your defense organization as soon as possible following the incident. MT

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MCR110413MYb

Experimental therapies to shape future of CHB management

Christina Lau

The future of chronic hepatitis B (CHB) management lies in enhancing the reversal of fibrosis and increasing the rate of hepatitis B surface antigen (HBsAg) seroconversion, said an expert at the recent International Symposium on Hepatology 2013 and 26th Annual Scientific Meeting of the Hong Kong Association for the Study of Liver Diseases.

"HBsAg seroclearance is the ideal endpoint in CHB treatment. However, it is achievable in only about 10 percent of patients with currently available nucleos[t]ide analogs [NAs] and interferon [IFN]," said Professor Ching-Lung Lai of the Department of Medicine, University of Hong Kong.

The alternative endpoint is permanent suppression of hepatitis B virus (HBV) DNA to a level undetectable by polymerase chain reaction assays, he suggested.

"Future therapies for CHB will involve agents that can potentially hasten the reversal of fibrosis and bring about greater reductions in HBsAg levels," he said.

For example, a monoclonal antibody against connective tissue growth factor (CTGF) was found to block peritoneal fibrosis in neonate mice. "CTGF is an active mediator of fibrogenesis. Suppression of CTGF expression improved fibrosis in pharmacological models," explained Lai. "The monoclonal antibody, known as FG-3019, is in a phase II clinical trial in 91 HBV patients with various stages of fibrosis. It's well tolerated in all populations tested."

Other novel therapies in development include a small interfering RNA (siRNA) against HBV known as ARC-520, HBV core inhibitors, and a nucleotide analog called besifovir.

"ARC-520 is being evaluated in a single-center phase I study of 36 patients, with no adverse events reported so far. A phase IIa study is scheduled to start in 2014," said Lai. "In lamivudine-treated chimpanzees, two doses of ARC-520 reduced HBsAg by 81 percent, hepatitis B e antigen by 89 percent, and HBV DNA by 30 fold."

"Core proteins play an important role in HBV replication. HBV core inhibitors in combination with NAs may provide greater inhibition of HBV DNA replication and covalently closed circular DNA [cccDNA] replenishment, and reduce intrahepatic reinfection," he continued. "Using core inhibitors with pegylated interferon may synergize the activation of innate immune response and cccDNA silencing."

Besifovir, a nucleotide analog of guanosine monophosphate, was shown to reduce HBV DNA levels by approximately 4 logs in lamivudine-resistant HBV patients (n=65)

following 12 weeks of treatment. [*Hepatology* 2010;51:767-776]

In a multicenter phase IIb study of 114 Asian patients, Lai and colleagues showed that up to 63.6 percent of besifovir-treated patients achieved undetectable HBV DNA at 48 weeks, compared with 58.3 percent of entecavir-treated patients. "The mean log HBV DNA reductions were significantly greater with both 90 mg and 150 mg besifovir vs entecavir," he reported. "The only significant side effect of besifovir was L-carnitine depletion, which was normalized with carnitine replacement." [*Gut* 2013. doi: 10.1136/gotjnl-2013-305138]

Before these novel therapies become available, clinicians will have to rely on the existing armamentarium of NAs and interferon. "NAs are superior to interferon in terms of efficacy, reversal of fibrosis and reduction of hepatocellular carcinoma," said Lai. [*Hepatology* 2013;57:399-408] MT

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Oral anticoagulants and antiplatelet drugs reduce risk of secondary VTE

Venous thromboembolism (VTE) is the third most common cardiovascular disorder. Although potentially fatal, it can be treated and prevented with anticoagulants, but there is a trade-off with the risk of major bleeding events.

A recent systematic review and network meta-analysis compared the efficacy and safety of the oral anticoagulants dabigatran (150 mg twice daily), rivaroxaban (20 mg/day), apixaban (2.5 mg and 5 mg twice daily), vitamin K antagonists (standard dose, target international normalized ratio [INR] 2.0–3.0; low dose, target INR 1.5–3.0), ximelagatran (24 mg twice daily), and an antiplatelet agent (acetylsalicylic acid 100 mg/day) for the secondary prevention of VTE. Literature searches of the Medline, Embase and Cochrane Register of Controlled Trials databases were performed to identify randomized controlled trials in which patients received anticoagulants, antiplatelet drugs, or placebo or observation. Twelve articles were identified and 11,999 patients were evaluated for efficacy and 12,167 for safety.

All treatments reduced the risk of recurrent VTE. Compared with placebo or observation, standard-dose vitamin K antagonists showed the greatest effect (odds ratio [OR] 0.07; 95% CI 0.03-0.15) followed by dabigatran (OR 0.09; 95% CI 0.04-0.21); acetylsalicylic acid had the smallest effect (OR 0.65; 95% CI 0.39-1.03). Among these three agents, the risk of major bleeding was highest for the standard-dose vitamin K antagonists (OR 5.24; 95% CI 1.78-18.25) versus placebo or observation. The corresponding odds ratios for dabigatran and acetylsalicylic acid were 2.79 (95% CI 0.79-11.69) and 1.29 (95% CI (0.4-4.08). Fatal VTE recurrence and major bleeding events were rare. MI

Castellucci LA et al. Efficacy and safety outcomes of oral anticoagulants and antiplatelet drugs in the secondary prevention of venous thromboembolism: systematic review and network meta-analysis. BMJ 2013; 347: f5133

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Treatments fail to reduce cough in acute bronchitis patients

Acute bronchitis is one of the most common complaints encountered by primary care physicians. The condition is primarily caused by viral infection and is generally self-limiting, but most patients continue to be prescribed antibiotic treatments, particularly if they report discoloration of sputum. Given the global increase in antibiotic resistance, this over-prescription is of concern. Since cough is the primary symptom of acute bronchitis, oral anti-inflammatory therapy has been suggested as a more appropriate treatment. However, a recent study in Spain has shown that neither oral anti-inflammatory nor antibiotic treatment is more effective than placebo at reducing cough frequency.

The prospective, parallel group, single-blind study included 416 adults aged 18-70 who presented with symptoms of respiratory infection of less than 1 week duration, predominately cough but also sputum discoloration and at least one of the following: dyspnea, wheezing, chest discomfort or chest pain. The patients were randomized to ibuprofen 600 mg three times daily (n=136), amoxicillin-clavulanic acid 500 mg/125 mg three times daily (n=137) or placebo three times daily (n=143) for 10 days. Symptom duration was assessed with a diary.

The median number of days with frequent cough was 9 (95% CI 8–10) among the ibuprofen recipients compared with 11 (95% CI 10-12) among those who received the antibiotic. However, this difference was not statistically significant. Moreover, the probability of cough resolution was not greater than that of placebo for both ibuprofen (hazard ratio [HR] 1.03, 95% CI 0.78–1.35) and amoxicillin-clavulanic acid (HR 1.23, 95% CI 0.93–1.61). MI

Llor C et al. Efficacy of anti-inflammatory or antibiotic treatment in patients with non-complicated acute bronchitis and discoloured sputum: randomised placebo controlled trial. BMJ 2013;347:f5762.

Suicide ideation in relatives bereaved by suicide

Relatives bereaved by suicide are known to be at increased risk of suicide themselves irrespective of whether they are genetically related to the deceased family member or friend. A recent study has indicated that this may be due to suicide ideation linked to symptoms of depression and complicated grief, which is a proposed clinical entity related to bereavement that is distinct from depression, anxiety and post-traumatic stress disorder. The study is unique in that it offers a long-term assessment of the course of bereavement.

The researchers analyzed data collected from a community-based sample of 153 first degree relatives and spouses of 74 individuals who committed suicide between September 1999 and January 2002 in the Netherlands. The participants completed self-report questionnaires assessing symptoms of complicated grief, depression, and suicidal ideation 2.5 months (baseline), 13 months, and 96-120 months (8–10 years) after the index suicide.

Suicide ideation, depression and complicated grief were strongly mutually associated. A total of 26 percent suffered from suicide ideation at baseline, compared with 9 percent at 96-120 months. Long-term suicide ideation was linked to a history of attempted suicide and was strongly associated with an increased risk of complicated grief and depression. However, these risks decreased over time. Long-term depression was more common among women and those with low levels of mastery. Parents who lost a child were at greater risk of complicated grief. Family-based therapy, support from a general practitioner, and/or mental healthcare did not affect the long-term course of bereavement. Mutual support provided by voluntary clergy- or peer-led groups was associated with an increased risk of complicated grief, but the researchers caution that this may be due to selection bias. MI

de Groot M & Kollen BJ. Course of bereavement over 8-10 years in first degree relatives and spouses of people who committed suicide: longitudinal community based cohort study. BMJ 2013; 347:f5519.Neal B. Trials in kidney disease – time to EVOLVE. Ibid:2541-2542 (editorial).

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Coffee consumption positively correlated with all-cause mortality

Given the popularity of coffee consumption worldwide it is of no surprise that a recent study linking coffee consumption with all-cause mortality has been the subject of much comment, particularly since no such association was observed with cardiovascular mortality.

In their study, the researchers evaluated observational data from 43,727 individuals aged 20-87 years who were enrolled in the prospective Aerobics Center Longitudinal Study. All completed a medical history questionnaire assessing their lifestyle habits and personal and family history and underwent a baseline medical examination between February 3, 1971 and December 30, 2002. Individuals with cardiovascular disease or cancer and those who were underweight or had abnormal electrocardiographic findings were excluded, which left 43,727 individuals (33,900 men and 9,827 women with 699,632 person-years of follow-up) who met the inclusion criteria and were observed for mortality from the baseline examination to their date of death or December 31, 2003.

A total of 2,512 deaths occurred during the median 17-year follow-up period. Multivariate analyses revealed an association between the consumption of >28 cups coffee/week and all-cause mortality in men only (hazard ratio [HR] 1.21; 95% CI 1.04-1.40). However, stratification by age indicated that coffee intake >28 cups/week was associated with all-cause mortality in both men and women younger than 55 years (men: HR 1.56, 95% CI 1.30–1.87; women: HR 2.13; 95% CI 1.26-3.59). Adjustments were made for age, baseline examination year, decaffeinated coffee use, regular tea use, decaffeinated or herbal tea use, physical inactivity, body mass index, smoking, alcohol consumption, diabetes, hypertension, hypercholesterolemia, family history of cardiovascular disease, and physical fitness.

The researchers stressed that further studies are needed to confirm their findings, but they caution that younger individuals may be better off avoiding excessive coffee consumption (average >4 cups/day). MT

Liu J et al. Association of coffee consumption with all-cause and cardiovascular disease mortality. Mayo Clin Proc. 2013; 88 (10): 1066-1074.

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Mixed microbial preparation offers no protection against AAD

Antibiotic-associated diarrhea (AAD) is a common complication among inpatients aged ≥65 years treated with broad-spectrum antibiotics, which is concerning since Clostridium difficile–induced AAD (CDD) can be life-threatening. A variety of microbial preparations have been tested with the aim of ameliorating or preventing AAD and CDD by restoring the gut microbial flora, but their efficacy remains controversial. Recently, a multicenter efficacy trial found no evidence of any protective effect of a multistrain lactobacilli and bifidobacteria preparation against AAD or CDD.

The double-blind study evaluated 2,981 inpatients aged ≥65 years who were randomized to receive the microbial preparation containing 6×1010 live bacteria (n=1,493) or placebo (n=1,488) once daily for 21 days. All patients had been exposed to one or more antibiotics in the preceding 7 days or were about to begin antibiotic treatment. Follow-up was for 8 weeks.

A modified intention-to-treat analysis of 2,941 participants revealed that AAD (including CDD) occurred in 10.61 percent of patients, and the incidence was similar between the treatment and placebo groups (relative risk [RR] 1.04, 95% CI 0.84-1.28). Moreover, CDD was only observed in 0.99 percent, and again the incidence was similar in both groups (RR 0.71, 95% CI 0.34-1.47). The microbial preparation did not appear to have any protective effect against diarrhea severity, frequency of abdominal symptoms, length of hospital stay or quality of life. The researchers commented that a better understanding of the pathophysiology of AAD is required. MT

Allen SJ et al. Lactobacilli and bifidobacteria in the prevention of antibiotic-associated diarrhoea and Clostridium difficile diarrhoea in older inpatients (PLACIDE): a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2013; Aug 7 pii: S0140-6736(13)61218-0. doi: 10.1016/S0140-6736(13)61218-0 [Epub ahead of print]

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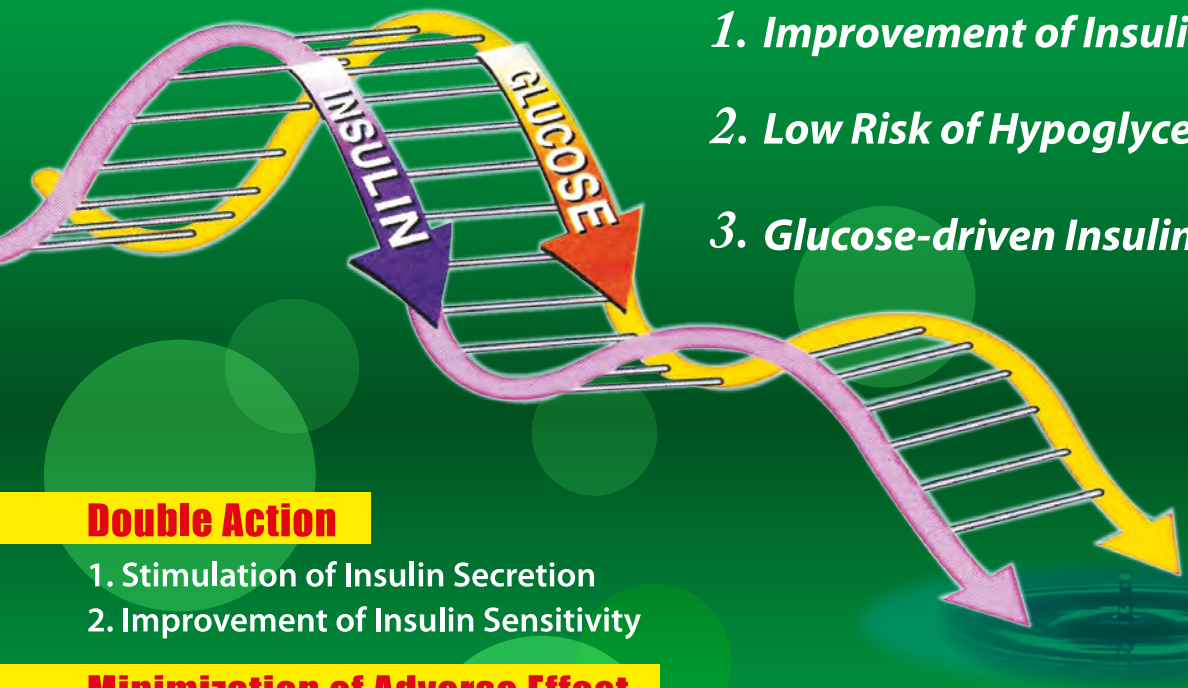

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Sulphonylurea ADVANCEs:
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The advent of new classes of oral antidiabetic drugs (OADs) signals a need to redefine the role of existing treatment options in the management of type 2 diabetes (T2D). To address this, Servier invited Professor Antonio Ceriello for the NADI Diabetes Asia 2013 conference to share his views on the clinical relevance of gliclazide and how it benefits T2D patients.

Professor Antonio Ceriello
Head of Research
Department of Diabetes and Cardiovascular Disease
Intitut d'Investigacions Biomédiques August Pi I Sunyer
Barcelona, Spain

Reducing microvascular complications and more importantly, cardiovascular (CV) mortality and morbidity, are important goals in diabetes care. Although the evidence for reduction of microvascular complications with good glycaemic control is robust[1-7], many of these trials failed to demonstrate favorable CV benefits, which are only evident after long periods of follow up.[1-4]

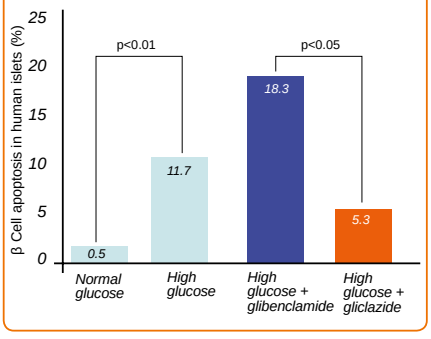
As a class, sulphonylureas (SUs) have been recommended to be suitable as an alternative first line to metformin[8] or in combination with metformin to achieve glycaemic control.[8,9] "While some of these recommendations (metformin, SUs and insulin) are backed by evidence of clinical benefits,[3,4] others classes of OADs have yet to demonstrate CV protection," stressed Prof Ceriello.

SUs: debunking the myths

β cell exhaustion

The UKPDS revealed that worsening of hyperglycaemia is a relentless process - progressive decline in *β* cell function is similar irrespective of the type of antidiabetic therapy administered.[10] Hyperglycaemia is a state of increased oxidant stress which in turn, causes *β* cell apoptosis. A preclinical study found that gliclazide possesses antioxidant properties.[11] Del Guerra et al went on to demonstrate that it was these antioxidant properties of gliclazide which protected human *β* cells from apoptosis induced by intermittent high glucose (**Figure 1**).[12]

Figure 1. Gliclazide inhibits β cell apoptosis[12]



Clinically, the study by Satoh et al demonstrated that treatment with gliclazide significantly delayed the time to onset of insulin treatment compared to glibenclamide therapy, which could be due to the protective benefits of gliclazide against secondary beta cell failure.[13]

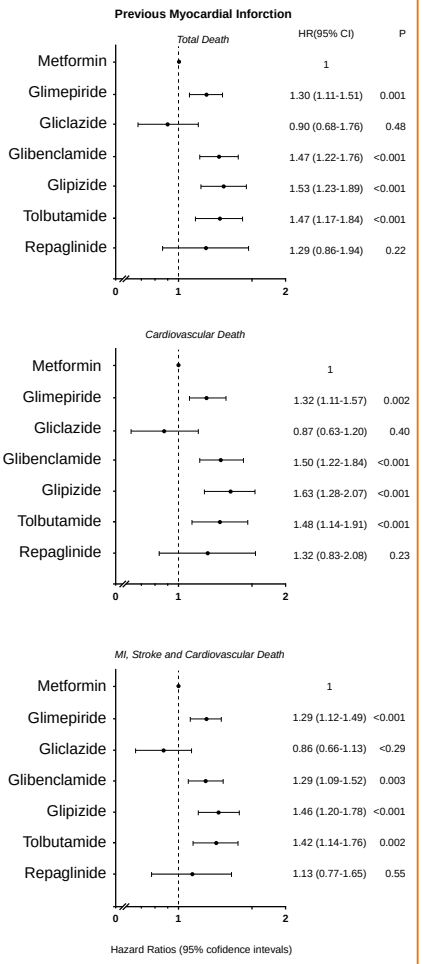
Adverse CV effects

Older SUs have been linked to adverse CV effects. An early comparison by Johnsen et al found that newer SUs, including gliclazide, are associated with lower risk of myocardial infarction (MI).[14] Schramm et al recently concurred with this finding as well – gliclazide is associated with lower incidences of mortality and CV risk compared to other insulin secretagogues (**Figure 2**).[15] Similarly, the BARI 2D trial which compared two antidiabetic approaches i.e. insulin-sensitization vs. insulin-provision, did not find any significant difference between both approaches in terms of CV mortality rates.[16] Meanwhile, the ADVANCE trial has shown that intensive therapy with gliclazide modified-release (MR) is associated with a trend in reduction of CV death (**Figure 3**).[6] "Since ADVANCE is still an on-going trial, it would be interesting to see if gliclazide MR on long-term follow-up can provide secondary CV prevention benefits in patients with previous history of CVD and long-standing T2D," highlighted Prof Ceriello.

High rates of hypoglycaemia

A comparison of gliclazide MR and glimepiride found that while both agents are equally efficacious in improving long-term glycaemic control, gliclazide MR has significantly lower (50% less) hypoglycaemic episodes.[17] The ADVANCE trial highlighted the effectiveness of a gliclazide MR-based regimen in achieving HbA_{1c} goals – the majority of patients achieved $HbA_{1c} \leq 7.0\%$, while 65% had $HbA_{1c} \leq 6.5\%$. Low rates of severe hypoglycaemia were also demonstrated with the gliclazide MR regimen, i.e., 0.7 events/100 patients/year (**Figure 4**).[6] Additionally, two studies which looked at rates of hypoglycaemia in fasting diabetic patients during Ramadan found similar rates of symptomatic hypoglycaemia with gliclazide compared to sitagliptin - Al Sifri et al, gliclazide 6.6% vs. sitagliptin 6.7%[18] and Aravind et al, gliclazide 1.8% vs. sitagliptin 2.1%.[19]

Figure 2. Mortality and CV risk with insulin secretagogues vs. metformin in type 2 diabetes with previous MI



Adapted from: Schramm TK, et al. *Eur Heart J* 2011;32(15):1900-1908.

Gliclazide and the metabolic memory

Metabolic memory refers to diabetic vascular stress which persists after glucose normalisation[20] and this phenomenon possibly explains the difference in CV benefits with intensive control seen in UKPDS compared to VADT, highlighted Prof Ceriello. It also underlines the need for early aggressive glycaemic control before metabolic memory has been established. The study by Corgnali et al demonstrated that metabolic memory arises as a result of oxidative stress brought on by prolonged hyperglycaemia and gliclazide attenuates this cellular memory, decreases oxidative stress and protects vascular endothelial cells from apoptosis.[21]

In conclusion

To summarise his presentation, Prof Ceriello reiterated that there are distinct differences among the SUs. As a compound, gliclazide has demonstrated antioxidant properties which protect beta-cells from apoptosis, is associated with CV protection benefits and has a hypoglycaemia profile similar to DPP4-inhibitors, a class of OADs typically associated with neutral effects on hypoglycaemia.

Figure 3. ADVANCE study - trend to reduction in CV death with Diamicron-based intensive control regimen[6]

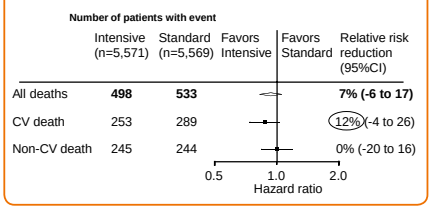
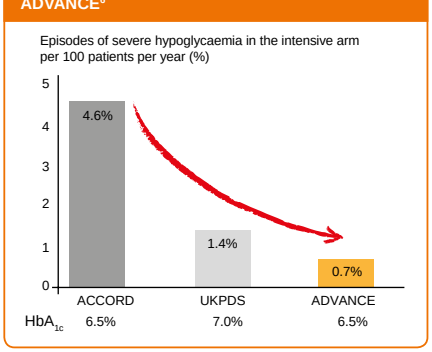


Figure 4. Incidence of hypoglycaemia was low in ADVANCE[6]



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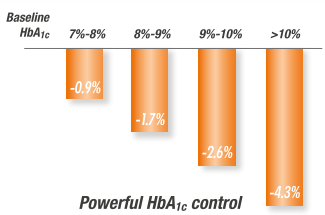

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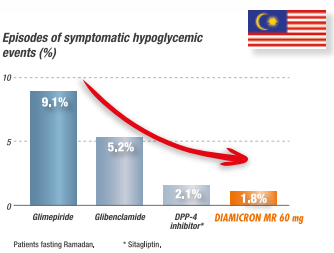

DIAMICRON MR 60 mg ensures low risk of hypoglycemia similar to sitagliptin[2]

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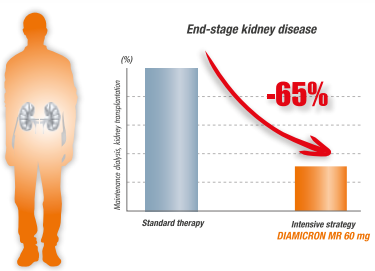

DIAMICRON MR 60 mg showed 65% less dialysis and kidney transplantation vs standard therapy[3]

Further information is available on request.

1. Zoungas S, et al. ADVANCE Collaborative Group. *Diabetes Res Clin Pract.* 2010;89:126-133. **2.** Aravind, et al. *Curr. Med Research & Opinion.* 2012;28(8):1-8. **3.** Zoungas S, et al. *Diabetologia.* 2011;54(suppl 1):S23.

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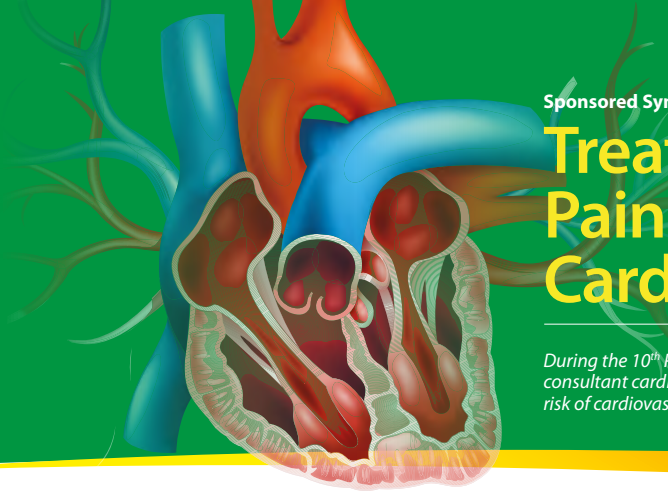

Sponsored Symposium Highlights

Treating Mild-to-Moderate Pain in Patients at Risk of Cardiovascular Events

During the 10th Primary Care Symposium held at Le Meridien Hotel, Kuala Lumpur, Dr Lim Bee Chian, a consultant cardiologist at the National Heart Institute, shared his recommendations on analgesia in patients at risk of cardiovascular (CV) events. During his talk, Dr Lim highlighted CV issues associated with NSAID use.

Dr Lim Bee Chian
Consultant Cardiologist
National Health Institute

Non-cardiac mild-to-moderate pain can be caused by many factors including, arthritis, headaches and migraines, menstrual pain, muscle soreness and dental procedures. In the US, the most commonly used analgesics, with more than 98 million prescriptions, are non-steroidal anti-inflammatory drugs (NSAIDs). However, NSAIDs should be used with caution as they are associated with the risk of bleeding, heart attacks and strokes. Annually, NSAIDs cause more than 100,000 hospitalizations and more than 16,000 deaths in the US.[1] Dr Lim cautioned that when prescribing NSAIDs, it is important to ensure that the patient is not at risk of CV disorders (CVD).

Treating mild-to-moderate pain – what is available?

There are several drugs, with different mechanisms of action, available for treating mild-to-moderate pain. Paracetamol (PCM) acts centrally. However, despite being a well- and commonly used medication, its mechanism of action is not fully defined. Aspirin irreversibly inhibits COX-1 (both at high and low doses) and COX-2 (at high doses). Non-selective NSAIDs (NS-NSAIDs) are COX-1 and COX-2 competitive inhibitors. Coxibs selectively compete for inhibition of COX-2.[2]

Cardio-renal and gastrointestinal (GI) toxicity

Non-aspirin NSAIDs are associated with CV events. Dr Lim advised that patients at risk for NSAID-related CV events include those that have:

- **History of chronic heart failure (CHF)[3]**
- **History of hypertension[4]**
- **Been taking anti-hypertensives or diuretics[5]**
- **Elderly with co-morbidities and polypharmacy.[10]**

Use of NSAIDs (other than low-dose aspirin) is associated with the doubling of odds of hospital admission with CHF. In patients with a history of heart disease, the odd ratio was 10.5 for first admission with HF, compared with 1.6 in those without such history. The burden of illness resulting from NSAID-related CHF may exceed that of GI damage and NSAIDs should therefore, be used with caution in patients with history of CVD.[3]

Interaction with ibuprofen, an NSAID, limits the cardioprotective properties of aspirin. In patients with high CV risk, it would be advisable that they avoid chronic ibuprofen use.[6] In this situation, PCM should be considered as it does not interfere with the inhibition of platelet aggregation by aspirin.

Coxibs and NS-NSAIDs have similar renal risk profiles: both reduce glomerular filtration rate and are associated with a risk of acute renal failure in certain patient population.[7] A study found that edema and destabilized blood pressure (BP) led to discontinuation of coxibs in 58 – 82% of cases.[8] The renal effects seen with NSAIDs and coxibs can be attributed to the inhibition of prostaglandin synthesis.[9]

Dr Lim highlighted that NSAIDs have the potential to increase BP in patients treated with anti-hypertensives. For analgesia, PCM should be considered as an alternative to NSAIDs in patients with increased risk of high BP, stroke, CHF or impaired kidney function.[5] This is in line with recommendations from the American Geriatric Society[10] and American Heart Association.[11]

Numerous studies have shown that taking NSAIDs increase the risk of stomach bleeding. In patients at risk of CVD, the risk of GI events is amplified when NS-NSAIDs/ coxibs are co-administered with aspirin.[12] For these patients, PCM should be considered as it does not significantly increase risk of GI events either as monotherapy[13] or in combination with aspirin.[14]

Summary

NSAIDs are associated with cardio-renal and GI toxicity, especially in populations that have high CV risk. To provide effective analgesia for mild-to-moderate pain in this special population of patients, Dr Lim advises that PCM should be considered.

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In My Opinion...

Comments from Dr Ng Wai Kiat, Consultant Cardiologist

Dr Ng Wai Kiat
Consultant Cardiologist
Pantai Hospital, Kuala Lumpur

What are your key concerns when prescribing a pain reliever to a OA patient with CVD? How do you overcome these concerns?

Using analgesics in elderly patients with osteoarthritis or patients with CV disease can sometimes result in dire complications. I have often seen NSAIDs prescribed to these patients without looking into their CV risk.

I have encountered patients prescribed only a short course of NSAID or COX-2 inhibitors that resulted in impaired renal perfusion, increased blood pressure and cardiac failure. It is important that renal function and blood pressure be monitored in subjects taking NSAID/COX-2 inhibitors, and extra caution be used should these drugs be given to subjects with preexisting hypertension, renal disease, and heart failure.

I personally would use paracetamol or tramadol as first line to control osteoarthritic discomfort, failing which I would opt for naproxen as it may be the safest for people with CV disease. It is important to start with the lowest dose necessary to control symptoms and prescribe for the shortest time possible. For the elderly CV patient who is already taking low dose aspirin and requires an NSAID, I would add in a proton-pump inhibitor to decrease the risk of gastrointestinal bleed.

Do you apply the same principles in treating pain amongst patients who do not have CV co-morbidities?

In those with low or no CV risk, the analgesic choice could be more liberal, but it is always more prudent to do a stepwise escalation of the analgesic.

Have you got any advice that you would like to share with GP's on pain management?

Treatment of chronic pain poses a challenge for all primary care doctors because of the possible heightened risk of heart attack and stroke in patients taking NSAIDs and COX-2 inhibitors. Paracetamol is a suitable alternative to NSAIDs, as it has a low incidence of adverse effects, and should be the preferred choice in high-risk patients.

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"Paracetamol is recommended for musculoskeletal symptoms in patients with known CV disease or risk factors for ischemic heart disease" *The American Heart Association*[1]

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Nutrition, early development to be research focus of new institute

Rajesh Kumar

The role of nutrition and early development in the onset and progression of obesity and diabetes among Asians will be the research focus for the newly established Singapore Centre for Nutritional Sciences, Metabolic Diseases, and Human Development (SiNMeD).

The $148 million institute is a collaboration between the National University of Singapore (NUS) Yong Loo Lin School of Medicine and A*STAR's Singapore Institute for Clinical Sciences (SICS).

Its key research programs are: early development, which will focus on mother and infant nutrition, growth and developmental epigenetics; nutritional sciences, which aim to develop strategies for optimal nutrition; and metabolic diseases, which will study obesity and insulin resistance in Asians.

The programs will build on existing collaborations that have attracted significant investments from major food and nutrition companies such as Nestlé, Abbott and Danone. They will expand on the success of the GUSTO (Growing Up in Singapore Towards healthy Outcomes) birth cohort study, as well as work by the EpiGen consortium – an alliance of leading epigenetics researchers from the UK and New Zealand.

GUSTO is one of the world's most comprehensive birth cohort studies involving over 1,200 families, where women were recruited during pregnancy and followed until their infants were at least 3 years of age. Data was collected on a range of environmental exposures in parents and their offspring to evaluate the role of developmental factors in metabolic diseases.

The new institute will research mother and infant nutrition and its effects on growth and development.

"SiNMeD's research will help us to understand how the food we eat can lead to epigenetic changes in our DNA, which will in turn, either protect or predispose us to diseases like obesity and diabetes. This opens up new approaches to prevent and treat these diseases," said Dr. Benjamin Seet, executive director of A*STAR's Biomedical Research Council.

"Our knowledge of how optimal nutrition and lifestyle can delay or prevent disease onset in Asians is sadly lacking. SiNMeD will pool the expertise of NUS and A*STAR to greatly improve our knowledge of this area, to the betterment of society," added NUS Deputy President (Research and Technology) and Tan Chin Tuan Centennial Professor Bar-

ry Halliwell.

A $25 million metabolic Translational and Clinical Research (TCR) Flagship program grant awarded by the National Research Foundation in 2008 brought clinical investigators from the National University Health System, KK Women's and Children's Hospital, Singapore General Hospital and Tan Tock Seng Hospital together with researchers from SICS and other A*STAR research institutes for the GUSTO study, now culminating in SiNMeD. MT

Meal replacement may help control weight in diabetes

Rajesh Kumar

Half of the 407 overweight diabetics who also had problems controlling their weight said, in a recent survey, that they would consider a diabetes-specific meal replacement to aid weight loss and to manage their blood sugar levels.

Commissioned by Abbott Nutrition, the survey polled people with diabetes and a body mass index (BMI) of ≥25 in an effort to understand their awareness and attitudes towards the diagnosis, treatment and management of their condition.

It revealed that the patients had poor control of their weight and blood sugar. Poorly managed diabetes can lead to death and disability through long-term complications including blindness, kidney failure, coronary heart disease and stroke.

Good control of blood sugar levels is the best way to prevent or delay the onset of such complications, said Dr. Kevin Tan, consultant endocrinologist and vice-president of the Diabetic Society of Singapore. Weight loss, in combination with a healthy diet and regular exercise, can help.

The survey showed that even at prediabetes stage (impaired fasting glucose or impaired glucose tolerance), some patients either did not try or did not succeed in losing weight to ward off diabetes despite being aware of the risk.

The implication of the above findings is that if meal replacements can help patients ward off diabetes or achieve a better control of their condition, they should be offered the choice alongside other lifestyle and/or pharmaceutical interventions.

Some overweight patients with diabetes may successfully lose weight initially, but may eventually hit a plateau and find it difficult to shed the extra kilos, said Ms. Magdalin Cheong, chief dietician and assistant director of Dietetic & Food Services at Changi General Hospital, Singapore.

"For patients with such difficulties, adopting a treatment plan that includes a diabetes-specific meal replacement as part of a structured diet over a limited period is a good alternative," said Cheong.

However, one-third of the survey respondents indicated that they would not consider using a meal replacement, citing perceived cost as the main issue. At a media conference organized to share the survey findings,

Abbott quoted studies to counter the concern saying that it could actually be cost-effective in the long-term.

"Replacing a meal with a diabetes-specific meal replacement not only provides nutritional value but could also translate into cost savings in the long-run. For example, the cost of a meal replacement is comparable to the price of a standard meal, but it is definitely a healthier option," said Tan. MT

Project NEMO benefits patients with diabetic kidney disease

Elvira Manzano

A coordinated primary-tertiary care diabetes program in Singapore has helped thousands of patients with diabetic kidney disease (DKD), a common complication of diabetes, improve renal function and prevent or delay disease progression.

Two years into the launching of Project NEMO [Nephrology Evaluation Management and Optimization], a collaborative effort between the National Healthcare Group Polyclinics and the National University Hospital, close to 24,000 diabetics have been screened for kidney disease. Roughly about 4,200 were enrolled in the program and started on renal-protective medication, said Dr. Lim Chee Kong, co-program director of NEMO and deputy clinical director of Clinical Services, NHGP.

Of 1,497 DKD patients who had completed optimal treatment with angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARBs), 40 percent regressed to normoalbuminuria or improved from macro to microalbuminuria. Currently, 2,700 patients are on optimal therapy with appropriate safety monitoring and 886 are being evaluated for suitability to maximal dosing. Lim said only 3.7 percent progressed to advanced DKD.

Photo courtesy of the National Healthcare Group Polyclinics

NEMO coordinator Ms. Samantha Lim counsels patient Mdm. Susila about the importance of medication adherence and appropriate diet.

The prevalence of diabetes among Singaporeans aged 18 to 69 years was 11.3 percent in 2010, according to the 2010 National Health Survey. Even when the disease is controlled, a significant proportion of patients will develop chronic kidney disease (CKD) or progress to end-stage renal disease (ESRD).

In 2012, Singapore ranked second in the world in terms of ESRD incidence. Cases doubled from 246 in 2009 to 598. At Singapore's National University Hospital (NUH), 69 percent of new ESRD cases were due to DKD, said Professor Anantharaman Vathsala, pro-

gram director of Project NEMO and head and senior consultant, Division of Nephrology, NUH. "We need to do something before it's too late, and it has to start in primary care."

Additionally, one-third of diabetics being seen in polyclinics have early stage DKD and is at risk of progressing to advanced stages, Lim said. "It is important to start treatment early and manage their condition. Through this joint partnership with NUH, and with the support of the Ministry of Health, we hope to continue slowing down DKD progression, improve treatment outcomes for patients and improve their quality of life."

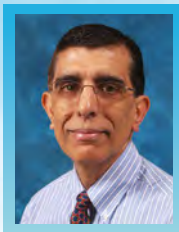
Currently, there are nine NEMO coordinators working with doctors on the project. Training was provided by NUH. Part of the job is to provide counseling (dietary restrictions, medication side effects), remind clinic appointments, and keep track of patients' progress.

Dr. Loh Ping Tyug, a NEMO program director and consultant at the Division of Nephrology, National University Health System, said they hope to roll out NEMO in as many polyclinics, and eventually GP clinics. MT

Bronchodilators in COPD Management:

Leading Respiratory Forward

During the *"Leading Respiratory Forward… Celebrating 10 years of Spiriva"* event in May 2013, held at Rasa Sayang Resort, Penang, Professor Anzueto from the US presented on the history and future of bronchodilators in the management of COPD.



Antonio Anzueto MD
Professor of Medicine
University of Texas Health Science Center
Texas, US

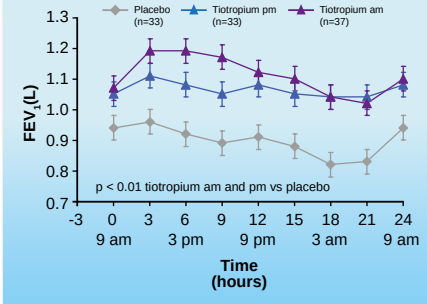
Role of Anticholinergic in COPD

Chronic obstructive pulmonary disease (COPD) pathophysiology may involve increased cholinergic tone, smooth muscle abnormalities and non-reversible airway components. The airway smooth muscle tone has been found to be primarily sustained by cholinergic activity, which may be increased in COPD. Therefore, the use of anticholinergic agents to inhibit this cholinergic activity is a logical and preferred therapeutic means of increasing airflow in COPD.[1]

Acetylcholine stimulates cholinergic receptors, which can be divided into nicotinic and muscarinic receptors. Tiotropium (Spiriva®) is an example of an anticholinergic agent that acts through prolonged M3 muscarinic receptor blockade.[1]

A double-blind, randomised, placebo-controlled trial found that not only does the once-daily administration of tiotropium 18 µg increase daytime FEV_1 in COPD, it also modifies the overnight change in FEV_1, regardless of the timing of drug administration. In other words, tiotropium produces sustained bronchodilation throughout the 24-hour day without necessarily abolishing the circadian variation in airway caliber (**Figure 1**).[2]

Figure 1: Improvement FEV1 over 24 hours by cholinergic blockade[2]



Analyses of long-term treatment suggest that tiotropium reduces the occurrence of exacerbations and may also slow the decline in lung function. Professor Anzueto postulated that these beneficial effects may be related to the sustained 24-hour airway patency. By maintaining airway patency, the decline in lung function may be prevented by reducing mechanical stress on the airway walls. Although exacerbations may still occur, the healing of the lung is not hampered and, thus, the decline in lung function is slower.[1]

In conclusion, effective 24-hour bronchodilation has a favorable impact on COPD symptoms, as well as on disease progression.

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10 Years of Spiriva

Our knowledge of COPD has evolved within 10 years, due to the change in patients' demographic characteristics, results of large clinical trials and new endpoints such as exacerbations. As a result, the Global Initiative for Chronic Obstructive Lung Disease (GOLD) recommendations have been updated to reflect the new findings.[1]

COPD is no longer just a disease seen in elderly men. Over the years, mortality rates for COPD have increased among women,[2] and a large percentage of COPD patients are below the age of 65.[3] It is time for a change in the management strategy: by tackling the root cause and fundamentally shifting the way we treat COPD. Not only should management of COPD include achieving current control (defined by symptoms, health status and lung function), but it should also aim to reduce future risks (defined by exacerbations, disease progression and mortality).[1]

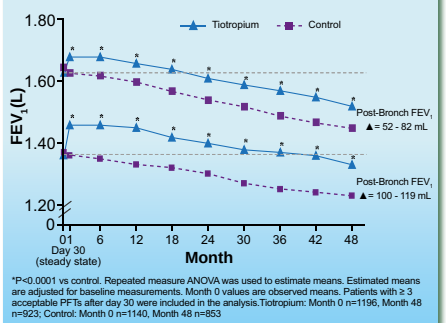
Hence long term studies, such as the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, paint a better picture of COPD treatment.

The UPLIFT trial compared four years of therapy with either tiotropium or placebo in patients with COPD who were permitted to use all respiratory medications except inhaled anticholinergic drugs. The investigators found that long-term use of tiotropium was associated with improvements in lung function, quality of life as well as exacerbations.[4]

In addition, tiotropium was associated with sustained reductions of lung hyperinflation, both at rest and during exertion. As a result of the increases in inspiratory capacity, there is greater expansion of tidal volume and improvements in both exertional dyspnea and exercise endurance.[5]

Recent data have suggested that the annual decline in FEV_1 is greater in GOLD stage II than in later stages of the disease. Hence, it is logical that intervention, aimed at reducing the progression of the disease, should start at the early stages of the disease. The UPLIFT trial showed that in patients with GOLD stage II COPD, long-term treatment with tiotropium reduced the rate of decline of postbronchodilator FEV_1 and the risk of exacerbations (**Figure 2**). Since lung function and quality of life were also better in the tiotropium group, the result supports the initiation of tiotropium in symptomatic patients with moderate disease.[6]

Figure 2: UPLIFT: Gold Stage II: Lung Function[6]



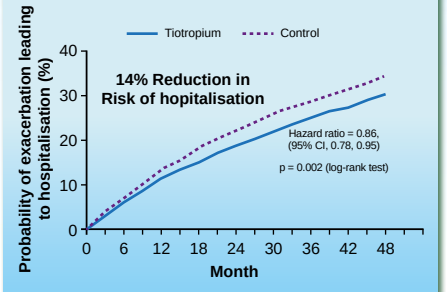
*P<0.0001 vs control. Repeated measure ANOVA was used to estimate means. Estimated means are adjusted for baseline measurements. Month 0 values are observed means. Patients with ≥ 3 acceptable PFTs after day 30 were included in the analysis.Tiotropium: Month 0 n=1196, Month 48 n=923; Control: Month 0 n=1140, Month 48 n=853

Moreover, a recent study showed that tiotropium once daily is effective over four years within all four of the newly-defined GOLD ABCD severities.[7] This is a step forward as many major studies in COPD were conducted based on the severity grading of lung function only.

Exacerbation is yet another important key event in COPD that needs to be targeted in the disease management. Exacerbations become more frequent and more severe as the severity of COPD increases; and the most important determinant of frequent exacerbations is a history of exacerbations.[8]

Tiotropium has been shown in various studies to significantly reduce exacerbation rates and delay the onset of first exacerbation.[9-11] The probability of COPD exacerbation leading to hospitalisation is also reduced with tiotropium (**Figure 3**). This result demonstrates the efficacy of tiotropium in preventing future events.[4]

Figure 3: Probability of COPD Exacerbation Leading to Hospitalisation[4]



When compared with salmeterol in the Prevention of Exacerbations with Tiotropium in COPD (POET-COPD) trial, tiotropium increased the time to the first exacerbation with a 17% reduction in risk (p<0.001) and decreased the annual rate of exacerbations among patients with moderate-to-very-severe COPD (p=0.002).[12]

Lastly, as witnessed in the UPLIFT trial, tiotropium reduces the risk of mortality by 16% compared to placebo (based on on-treatment analysis).[4]

While more bronchodilators appear in the market, tiotropium remains the gold standard in the management of COPD. Not only has tiotropium been shown to improve current control with improvements in symptom and lung function, it is also effective in reducing exacerbation and impacting disease progression.

In the last 10 years, studies on tiotropium have shown:

- Increased lung function declines in moderate patients.
- Improved quality of life and decreased exacerbations.
- Reduction in mortality.
- No increase in cardiovascular (CV) side effects.

Professor Anzueto concluded the presentation by reminding clinicians that the future of COPD management is in their hands. What they achieve now will affect their COPD patients in the future.

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New Long-acting Bronchodilators

Long-acting beta2-agonists (LABAs), as well as long-acting anticholinergics, are recommended as first choice for COPD patients in group B of the GOLD patient group. Beta2-agonists relax the smooth muscles of the airway by stimulating the beta2-adrenergic receptors, which increases cyclic AMP and produces functional antagonism to bronchoconstriction.[1]

LABAs such as salmeterol compare favorably with other bronchodilators such as ipratropium bromide in terms of effects on lung function at clinically recommended doses, due to its longer duration of action (12 hours).[2] Currently several ultra-LABAs with longer duration of action (24 hours) are under development. The longer dosing intervals, which may enhance compliance, encourage administration of these long-acting drugs in patients with COPD. One of these ultra-LABAs is olodaterol.

Olodaterol is a novel, inhaled beta2-adrenoceptor agonist with a 24-hour-long duration of action. *In vitro*, olodaterol shows a potent, nearly full agonistic response at the hβ2-AR and a significant selectivity profile. It exerts a weak partial agonism at hβ1-AR.[3]

According to Professor Anzueto, the clinical development of olodaterol is different from previously-approved LABAs because the principle development of olodaterol has been in COPD, instead of asthma.

Second phase trials found that all doses of olodaterol (2, 5, 10, 20 µg) provided significantly greater bronchodilation than placebo over 24 hours. A clear dose-response relationship was observed, with values ranging from 0.070 L for olodaterol 2 µg to 0.119 L for olodaterol 20 µg. Olodaterol also provided similar plasma concentration-time profiles over all dose groups, with no plasma levels detected following the 2 µg dose in most patients.[4]

The dose-finding studies were based on pharmacodynamics (safety) rather than just arbitrary efficacy threshold, while avoiding supratherapeutic dosing.

The Phase 3 clinical trials are ongoing to examine the efficacy and safety of olodaterol monotherapy, its 24-hour effect on lung-function and its effects on exercise. The investigators also seek to provide evidence of benefit in patient-relevant outcomes such as health-related quality of life, shortness of breath and rescue medication use.

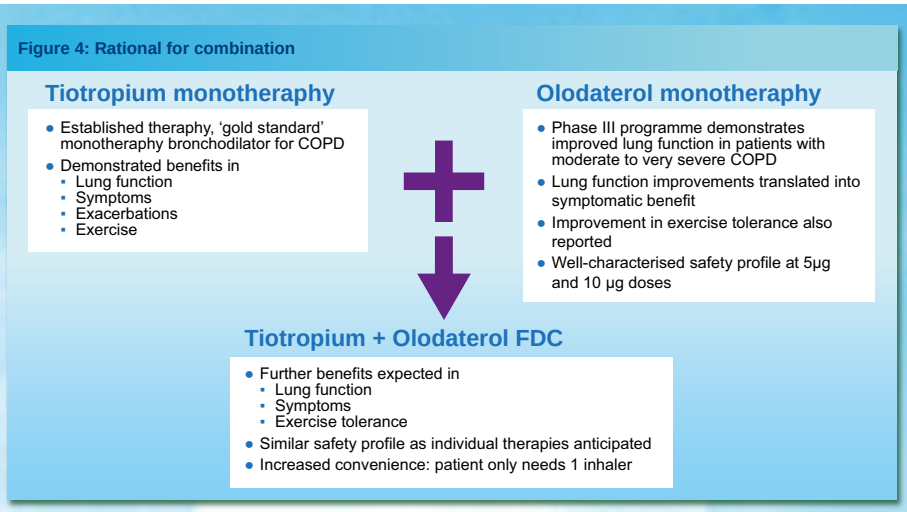
While the trials are in progress, it is good to know that the new LABA olodaterol has already been proven to:

- ▲ Have effect on cAMP:
  - Is potent, full agonist at hß2-AR.
  - Shows better selectivity.
  - Is partial agonist at hß1-AR.
- ▲ Show sustained bronchodilator effect.
- ▲ Have no tachyphylaxis.
- ▲ Have good safety profile.

The good efficacy and safety profiles of olodaterol justify its use in combination therapy. The GOLD report recommends the combination of beta2-agonists and anticholinergics if patient's symptoms are not improved with single agents.[1] According to Professor Anzueto, the rationale for combining long-acting bronchodilators lies in their synergistic effects, which may lead to the improvement in patient's quality of life outcomes. One of the latest promising fixed-dose combination (FDC) therapies is tiotropium + olodaterol.

Olodaterol has the properties of an ideal LABA partner for tiotropium. Since olodaterol is a potent β2-adrenoceptor agonist with high β2/β1 selectivity, it has the potential to provide optimal efficacy with reduced potential to cause adverse events and a low incidence of cardiovascular (CV) events. Olodaterol also has low potential for systemic exposure, with the additional benefit of long duration of action.[3,5] The rationale for the FDC is summarised in **Figure 4.**

Figure 4: Rational for combination


Tiotropium monotheraphy
Established theraphy, 'gold standard' monotheraphy bronchodilator for COPD
Demonstrated benefits in
Lung function
Symptoms
Exacerbations
Exercise
Olodaterol monotheraphy
Phase III programme demonstrates improved lung function in patients with moderate to very severe COPD
Lung function improvements translated into symptomatic benefit
Improvement in exercise tolerance also reported
Well-characterised safety profile at 5µg and 10 µg doses
Tiotropium + Olodaterol FDC
Further benefits expected in
Lung function
Symptoms
Exercise tolerance
Similar safety profile as individual therapies anticipated
Increased convenience: patient only needs 1 inhaler

Results of early phase II studies on tiotropium + olodaterol confirm the guideline recommendations of combined long-acting bronchodilator therapy for lung function and symptom improvements.

The main findings from phase II studies on tiotropium + olodaterol (5/10 µg) FDC demonstrated consistently superior bronchodilation compared to tiotropium (5 µg) alone over 24 hours following four weeks' once-daily dosing. There was a clear dose-response relationship for olodaterol within combination (tiotropium + olodaterol [5/2 µg] to tiotropium + olodaterol [5/10 µg]). No safety or tolerability concerns were identified.[6]

Results from the ongoing phase III trials, which evaluate the efficacy and safety of a free combination of tiotropium + olodaterol will no doubt be something to look forward to in months to come.

References: 1. GOLD. Global strategy for the diagnosis, management and prevention of COPD. Updated 2013. **2.** Matera MG, et al. *Pulm Pharmacol* 1995;8(6):267-271. **3.** Bouyssou T, et al. *J Pharmacol Exp Ther* 2010;334(1):53-62. **4.**Van Noord JA, et al. *Pulm Pharmacol Ther* 2011;24(6):666-672. **5.** Casarosa P, et al. *J Pharmacol Exp Ther* 2011; 337:600–609. **6.** Maltais F, et al. Poster presented at the ERS September 2010; Barcelona: 5557.

TIOSPIR™ Trial: Long-Term Safety of Tiotropium via Respimat and Handihaler

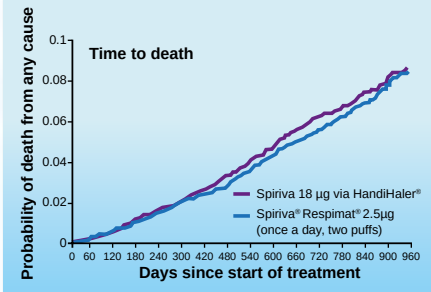
Tiotropium Safety and Performance in Respimat® (TIOSPIRTM) is a large scale, randomised, controlled, parallel-group trial that has recruited over 17,000 participants from over 1200 sites in 50 countries.[1] It was specifically designed to be of an adequate size and duration to closely reflect the real-world COPD patient population.

The study compared tiotropium Respimat® 5 µg and 2.5 µg once-daily to Spiriva® HandiHaler® (tiotropium bromide inhalation powder) 18 µg once-daily in COPD patients. The results were announced recently at the European Respiratory Society (ERS) Annual Congress 2013 in Barcelona, Spain.[2]

During a mean follow-up of 2.3 years, the investigators found that Respimat® was noninferior to HandiHaler® with respect to the risk of death (Respimat® 5 µg vs. HandiHaler®: hazard ratio, 0.96; 95% confidence interval [CI], 0.84 to 1.09; Respimat® 2.5 µg vs. HandiHaler®: hazard ratio, 1.00; 95% CI, 0.87 to 1.14) (**Figure 5**). Causes of death were similar in all treatment groups.[3]

Moreover, Respimat® was not superior to HandiHaler® with respect to the risk of the first exacerbation (Respimat® 5 µg vs. HandiHaler®: hazard ratio, 0.98; 95% CI, 0.93 to 1.03).[3] Results were also comparable for exacerbation frequency, as well as rate of COPD exacerbations associated with hospitalisation.[2]

Figure 5: Risk of death after treatment with Respimat® and Handihaler®[3]


Time to death
Probability of death from any cause
0.1
0.08
0.06
0.04
0.02
0
0 60 120 180 240 300 420 480 540 600 660 720 780 840 900 960
Days since start of treatment
Spiriva 18 µg via HandiHaler®
Spiriva® Respimat® 2.5µg (once a day, two puffs)

TIOSPIR™ also demonstrated that the incidence of adverse events and major adverse CV events was similar between the treatment groups. In patients with a history of cardiac arrhythmia, tiotropium Respimat® 5 µg and Spiriva® HandiHaler® 18 µg showed similar impact on survival as measured by all-cause mortality.[2]

In conclusion, tiotropium Respimat® at a dose of 5 µg or 2.5 µg has a safety profile and exacerbation efficacy similar to those of tiotropium HandiHaler at a dose of 18 µg in patients with COPD. The results from the landmark TIOSPIR™ trial reinforces the importance of Spiriva® in both available formulations as the world's leading maintenance therapy for COPD.

Summary from TIOSPIR™

This large-scale study that reflects real-world COPD population found that:

1. Respimat® 2.5 µg and 5 µg are not inferior to HandiHaler® 18 µg with respect to the risk of death.
2. Respimat® 5 µg is not superior to HandiHaler® 18 µg with respect to the risk of the first exacerbation. Rate of COPD exacerbations were also comparable.
3. Causes of death and incidences of major CV adverse events are similar in the three groups.

References: 1. Wise RA, et al. *Respiratory Research* 2013, 14:40-47. **2.** Landmark TIOSPIR™ trial demonstrates comparable long-term safety of tiotropium delivered via Respimat and HandiHaler in COPD patients. Press release archive. Boehringer Ingelheim website. **3.** Wise RA, et al. *N Engl J Med* 2013;369(16):1491-501.

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"The nurse in training will be with you as soon as she is finished catheterizing the patient next to you!"

"This is the part I dread the most!"

"Have you considered going to a tennis court rather than a food court?"

"The nurses are saying you are not swallowing your pills!"

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Reference:

1. Saruta T. et al. Antihypertensive Efficacy and Safety of Fixed-Dose Combination Therapy with Losartan plus Hydrochlorothiazide in Japanese Patients with Essential Hypertension. Hypertens Res 2007;30:729-739.
2. Schoenberger, JA. et al. Losartan with hydrochlorothiazide in the treatment of hypertension. J Hypertens Suppl. 1995 Jul;13(1):S43-7.
3. Data on file.

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Email : emergenmed@gmail.com
www.mma.org.my/MediaandEvents/EventsMarch2014/tabid/440/Default.aspx

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30th Annual Congress of the Malaysian Society of Nephrology
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www.hivnat.org/bangkoksymposium

6th Immunotherapeutics & Immunomonitoring Conference
29/1 to 31/1; California, US
Info : Global Technology Community
Email : infobiocbio@gtcbio.com
www.gtcbio.com

International Science Symposium on HIV & Infectious Diseases
30/1 to 01/02; Chennai, India
Info : Secretariat
Email : HIVSymposium@yrgcare.org
hivscience.yrgcare.org

FEBRUARY

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www.apch2014.com

3rd Global Congress for Consensus in Pediatrics & Child Health
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INTERNATIONAL EVENTS

MARCH

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Info : Secretariat
isge2014.isgesociety.com

5th Congress of Asia-Pacific Pediatric Cardiology Society
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Email : appcs2014@gmail.com
www.appcs2014.org

Asian Pacific Association for the Study of the Liver
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29/3 to 31/3; Washington D.C., US
Email : resource@acc.org
http://accscientificsession.cardiosource.org/ACC.aspx

16th Asia Pacific League of Associations Against Rheumatism
31/3 to 5/4; Cebu, Philippines
Email : aplar2014@kenes.com
http://aplarcongress.org/

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